CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
21-506

<u>MICROBIOLOGY REVIEW(S)</u>

Product Quality Microbiology Review
Review for HFD-590

23 FEBRUARY 2005

NDA: 21-506 and 21-754

Drug Product Name
Proprietary·   —   . MYCAMINE
Non-proprietary: micafungin sodium
Drug Product Priority Classification: S

Review Number: 2

Subject of this Review
Submission Date: 23 April 2004
Receipt Date: 26 April 2004
Consult Date: 10 June 2004
Date Assigned for Review: 23 February 2005

Submission History (for amendments only)
Date(s) of Previous Submission(s): 29 April 2002
Date(s) of Previous Micro Review(s): 23 January 2003

Applicant/Sponsor
Name: Fujisawa Healthcare
Address: Three Parkway North, Deerfield, IL 60015
Representative: Robert M. Reed
Telephone: 847-317-8985

Name of Reviewer: Bryan S. Riley, Ph.D.

Conclusion: Recommended for Approval

Product Quality Microbiology Data Sheet

A.   **1.**   **TYPE OF SUPPLEMENT:** N/A

     2.   **SUPPLEMENT PROVIDES FOR:** N/A

     3.   **MANUFACTURING SITE:**   Takaoka Plant
                                       Fujisawa Pharmaceutical Co., Ltd.
                                         30, Toide Sakae-machi
                                       Takaoka, Toyama 939-1118
                                       Japan

     4.   **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Sterile Lyophilized powder for IV infusion ⟶ 50 mg

     5.   **METHOD(S) OF STERILIZATION:**   —

     6.   **PHARMACOLOGICAL CATEGORY:** Anti-Fungal

B.   **SUPPORTING/RELATED DOCUMENTS:** 21-506

C.   **REMARKS:** The drug product in NDA 21-754 is identical to the drug product in NDA 21-506. This review covers the new information included in NDA 21-754 to address product quality microbiology deficiencies in NDA 21-506 (product quality microbiology review dated 23 January 2003). The rest of the manufacturing information references NDA 21-506 and is unchanged from the original submission.

filename: N021754R1.doc

Executive Summary

    I.   **Recommendations**

          A.   **Recommendation on Approvability** – These submissions are recommended for approval on the basis of product quality microbiology.

          B.   **Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – N/A

    II.   **Summary of Microbiology Assessments**

          A.   **Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – The drug product is   ---

          B.   **Brief Description of Microbiology Deficiencies** – N/A

          C.   **Assessment of Risk Due to Microbiology Deficiencies** – N/A

    III.   **Administrative**

          A.   **Reviewer's Signature** _____

          B.   **Endorsement Block**
                Bryan S. Riley, Ph.D. (Microbiology Reviewer)
                Microbiology Supervisor

          C.   **CC Block**
                N/A

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✓ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(5) Draft Labeling

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 5, 2005

TO: NDA #: 21-754 and 21-506

FROM: Shukal Bala, Ph.D.
Microbiology Team Leader
Division of Special Pathogen and Immunologic Drug Products (HFD-590)

SUBJECT: Micafungin

Introduction and Background:

The subject of this NDA is micafungin (FK463) an echinocandin with activity against 1,3-β-D-glucan synthase derived from *Candida albicans* and *A. fumigatus* but not mammalian cells. The preclinical studies supporting the activity of micafungin were reviewed earlier (for details see microbiology review dated 1-21-03, *,.* The clinical microbiologic evaluation of studies for the treatment of aspergillosis (FG 463-21-01 and 98-0-046) and candidiasis (FG 463-21-02, 98-0-47 and 97-7-003) was also included in the same microbiology review. In this submission the sponsor has included 2 clinical studies (FG 463-21-09 and 03-7-005) to support the efficacy of micafungin in patients with esophageal candidiasis. The primary microbiology review of this submission was assigned to Ms. Lynn Steele Moore. However, due to family emergency Ms. Moore was unable to complete the review. This microbiology team leader review discusses essential microbiologic findings abstracted from Ms. Moore's draft review of the study FG 463-21-09 and presents review of study 03-7-005 (not reviewed by Ms. Moore).

Clinical Microbiology:

Study FG 463-21-09 (information abstracted from Ms Moore's draft review):
This was a phase 2 dose ranging study of micafungin (50, 100, or 150 mg per day) in HIV patients with confirmed EC. Fluconazole (200 mg/day) was used as a comparator. A majority of the patients in the clinical trial were infected with *C. albicans*. Only 10 patients (4.6%) had *C. glabrata*, 4 (1.8%) had *C. tropicalis*, and 1 (0.5%) had *C. krusei*. Fifteen patients (6.9%) in this group were infected with more than one *Candida* species. There was no correlation of *in vitro* susceptibility of the baseline pathogen with clinical or microbiologic response.

The per protocol analysis of patients showed that both 100 mg and 150 mg doses appear to be better than 50 mg although mycological eradication was better in the 100 mg dose.

Study 03-7-005:
This was a phase III, randomized, double-blind, active control, multicenter study in patients with esophageal candidiasis from South Africa, Brazil, and Peru. Esophageal candidiasis was documented by clinical symptoms and confirmed by endoscopy. A majority of patients enrolled in the study had no prior history of esophageal candidiasis, had HIV, but did not receive antiretroviral therapy. CD4 cell count was <100 cells/ml in about 50% of the patients. In addition, tuberculosis was a frequent baseline condition. Micafungin (150 mg) or fluconazole (200 mg) were administered intravenously once daily for 14 days or for 7 days after resolution of clinical symptoms. Patients requiring treatment with another systemic or topical antifungal agent or those nonresponsive to prior systemic therapy were not eligible to participate in the study. The maximum duration of treatment was 42 days. Patients were evaluated at baseline, weekly, end of treatment (EOT; on day of last dose) and followed at 2 and 4 weeks after the last dose for clinical outcome which includes signs and symptoms for oropharyngeal candidiasis, laboratory parameters, and/or microbiologic response. Endoscopy was performed at EOT and follow up visits if clinically indicated. During endoscopy, mucosal lesions were biopsied and reviewed histologically. Esophageal brushings were obtained for cytological examination for fungal elements suggestive of yeast and cultured for identification of a fungal organism. Antifungal susceptibility testing was performed at centralized laboratory ⊦   ⸻
             ⸻   according to the NCCLS M27A2 method using antibiotic medium 3 and RPMI 1640 and minimum inhibitory concentrations (MICs) determined at 24 and 48 hours.

Per protocol population was defined as all patients who received at least 10 doses of study drug and who did not have major protocol deviation(s). A majority of the subjects in the micafungin (n=189) and flucanozole (n=192) treated groups were infected with *Candida albicans*. *Candida* species was not identified in 6 and 8 subjects in the micafungin and fluconazole treated groups, respectively. Infections with more than one *Candida* species were identified in 7 patients in the micafungin arm and 8 patients in the fluconazole arm. The results in Tables 1 and 2 show micafungin to be as effective as fluconazole in the treatment of patients with infections due to *C. albicans*. However, the number of patients with infections due to *Candida* species other than *C. albicans* was too small to conclude activity against these species. The activity of micafungin is sustained until week 4 after the last dose. At week 2 and 4 after the last dose, relapse was observed in 5% and 8% of the patients, respectively treated with micafungin; in patients treated with fluconazole relapse was observed in 4% and 6% of the patients at week 2 and 4, respectively. The fungal species at the time of relapse were not identified. Also, there was no correlation of *in vitro* susceptibility of the pathogen at baseline with clinical or microbiologic response.

Table 1: Clinical and mycological response by pathogen from patients with esophageal candidiasis to micafungin and fluconazole

Treatment Group	EOT **			Week 2**		Week 4**		Relapse*/**	
	Clinical Success	Eradication	Overall Response	Clinical Success	Mycological Success	Clinical Success	Mycological Success	Week 2	Week 4
Micafungin									
Candida sp.	6/6	5/6	5/6	6/6	0/0	5/5	0/0	ND	ND
C. albicans	173/175 (98.9%)	133/175 (76%)	131/175 (74.9%)	145/151 (96%)	2/12 (16.7 %)	137/144 (95%)	1/5	9/175 (5.1%)	14/175 (8.0%)
C. tropicalis	1/1	1/1	1/1	1/1	0/0	1/1	0/0	ND	ND
C. albicans + C. glabrata	4/4	0/4	0/4	4/4	0/4	3/3	0/0	ND	ND
C. albicans + C. tropicalis	1/1	1/1	1/1	1/1	0/0	1/1	0/0	ND	ND
C. albicans + C. glabrata + C. krusei	1/1	0/1	0/1	1/1	0/0	0/0	0/1	ND	1/1
C. albicans + C. inconspicua	1/1	1/1	1/1	1/1	0/0	1/1	0/0	ND	ND
Total	187/189 (98.9%)	141/189 (74.6%)	139/189 (73.5%)	159/165 (96.4%)	2/16 (12.5%)	148/155 (95.5%)	1/6 (16.7%)	9/151 (6%)	15/152 (9.9%)
Fluconazole									
Candida sp.	8/8	5/8	5/8	6/7	0/0	6/7	0/0	1/8	
C. albicans	173/175 (98.9%)	139/175 (79.4%)	139/175 (79.4%)	153/157 (97.4 %)	5/12 (41.7 %)	142/146 (97.3 %)	0/5	7/175 (4%)	11/175 (6.3%)
C. krusei	1/1	0/1	0/1	1/1	0/0	1/1	0/0	ND	ND
C. albicans + C. glabrata	3/3	1/3	1/3	3/3	0/0	3/3	0/0	ND	ND
C. albicans + C. krusei	2/2	2/2	2/2	2/2	0/0	1/1	0/0	ND	1/2
C. albicans + C. glabrata + C. krusei	1/1	0/1	0/1	1/1	0/0	1/1	0/0	ND	ND
C. albicans + C. glabrata + Candida sp.	0/1	0/1	0/1	1/1	0/0	1/1	0/0	ND	ND
C. albicans + C. tropicalis	1/1	0/1	0/1	1/1	0/0	1/1	0/0	ND	ND
Total	189/192 (98.4%)	147/192 (76.6%)	147/192 (76.6%)	168/173 (97.1%)	5/12 (41.7%)	156/161 (96.9%)	0/5	8/183 (4.4%)	12/177 (6.8%)

*Clinical relapse   ** n/N (%)   ND=Not Done

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Table 2: Clinical and mycological response by pathogen in patients with esophageal candidiasis treated with micafungin or fluconazole

Species	Micafungin*		Fluconazole*	
	Clinical Success n/N (%)	Mycological Eradication n/N (%)	Clinical Success n/N (%)	Mycological Eradication n/N (%)
C. albicans	180/182 (98.9%)	135/182 (74.2%)	180/183 (98.4%)	142/183 (77.6%)
C. glabrata	5/5	0/5	4/5	1/5
C. krusei	1/1	0/1	3/3	2/3
C. tropicalis	1/1	1/1	1/1	0/1
C. inconspicua	1/1	1/1	ND	ND

*includes patients with mixed infections

Conclusions:

Overall, the results from studies FG 463-21-02, 98-0-47, 97-7-003, and 03-7-005 show micafungin to be active against *C. albicans*, *C. tropicalis*, *C. glabrata*, *C. krusei*, and *C. parapsilosis* (Table 3).

Table 3: Clinical and mycological response by pathogen from patients treated with micafungin.

Species	Clinical Success n/N (%)	Mycological Eradication n/N (%)
C. albicans	287/307	211/297
C. glabrata	26/29	12/23
C. krusei	8/11	6/8
C. tropicalis	9/10	3/8
C. parapsilosis	7/10	7/8
C. rugosa	1/1	1/1
C. pelliculosa	1/1	1/1
C. guilliermondii	0/1	ND
C. kefyr	0/1	ND
C. inconspicua	1/1	1/1

From Ms. Moore's draft review of Study FG 463-21-09, the number of patients for which efficacy of micafungin was observed are unclear. Nevertheless, as described on page 2 the number of patients in study FG 463-21-09 with *Candida* species other than *C. albicans* is too small. Also, this does not alter the interpretation of activity of micafungin against *Candida* species other than *C. albicans*, *C. tropicalis*, *C. glabrata*, *C. krusei*, and *C. parapsilosis*.

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/s/

Shukal Bala
2/18/05 10:50:13 AM
MICROBIOLOGIST

DIVISION OF ANTIINFECTIVE DRUG PRODUCTS (HFD-520)
MICROBIOLOGY REVIEW
HFD-590 CONSULT
NDA 21-506   DATE REVIEW COMPLETED: 8 Oct 02

Review: Fred Marsik, Ph.D.

Date Company Submitted: 29 Apr 02   Date Assigned: 2 Aug 02

Sponsor: Fujisawa Healthcare, Inc.
Three Parkway North
Deerfield, IL 60015-2548

Robert M Reed
Associate Director, Regulatory Affairs
Phone:

Established Name: WF11899A, FK463, Micafungin sodium

Proprietary Name: Mycamine replaces   ⸺   (FDA memo 20 Sep 02)

Chemical Name: IUPAC: Sodium 5-[(1S,2S)-2-[3S,6S,9S, 11R,15S,18S,20R,21R,24S,25S,26S)-3-[(R)-2-carbomyl-1-hydroxyethyl]-11,20,21,25-tetrahydroxy-15-[(R)-1-hydroxyethyl]-26-methyl-2,5,8,14,17,23-hexaoxo-18-[4-[5-(4-pentyloxphenyl)isoxazol-3-yl]benzoylamino]-1,4,7,13,16,22-hexaazatricyclo[22.3.0.0^{9,13}]heptacos-6-yl]-1,2-dihydroxyethyl]-2-hydroxyphenyl sulfate

Empirical Formula: $C_{56}H_{70}N_9NaO_{23}S$

Molecular Weight: 1292.26

Drug Category: Antifungal

Proposed Indication: Prophylaxis of   ⸺   in patients undergoing hematopoietic stem cell transplantation

Dosage Form/Route of Administration: Liquid/Intravenous Infusion (not for IV bolus injection)

Proposed Dosage: For prophylaxis of '   ⸺   in patients undergoing hematopoietic stem cell transplantation:

Adults: 50 mg/day

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be followed

Supporting Documents: IND 55, 322

Background and Summary:

The Applicant has submitted this NDA to support the use of micafungin for the prophylaxis of   —   .   . . .
                                —   undergoing
hematopoietic stem cell transplantation. Micafungin is a water-soluble, semi-synthetic, lipopeptide of a new class of antifungal agents known as 1,3-beta-D-glucan synthase inhibitors. These agents inhibit the formation of the cell wall of susceptible fungi. Micafungin has structural similarities with echinocandin and pneumocandin derivatives. Other members of the class include caspofungin (Cancidas®) anidulafungin and cilofungin.

This submission is a priority review submission that was received by the Agency on April 29, 2002 and given to this Reviewer on August 2, 2002.

CONCLUSION:

It appears from in vitro data and the limited data provided by the Applicant from a pivotal study that micafungin has the potential to prevent fungal infections with *C. albicans*, certain *Candida* species and *Aspergillus fumigatus*. However, it is the feeling of this Reviewer that from the microbiology information provided in this Application that a final conclusion can not be made on the efficacy of micafungin

—— patients undergoing hematopoietic stem cell transplantation. More clinical data is needed.

DIVISION OF ANTIINFECTIVE DRUG PRODUCTS (HFD-520)
MICROBIOLOGY REVIEW
HFD-590 CONSULT
NDA 21-506   DATE REVIEW COMPLETED: 8 Oct 02

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EXECUTIVE SUMMARY

The Applicant has submitted this NDA to support the use of micafungin for the prophylaxis of ⎯ ⎯ , , persons undergoing hematopoietic stem cell transplantation (HCT). Micafungin is a water-soluble, semi-synthetic, lipopeptide of a new class of antifungal agents known as 1,3-beta-D-glucan synthase inhibitors. These agents inhibit the formation of the cell wall of susceptible fungi. This mechanism of action is different from the azole and polyene classes of antifungals in that those agents inhibit the formation of the cell membrane of fungi. Micafungin has structural similarities with echinocandin and pneumocandin derivatives. Other members of the class include caspofungin (Cancidas®) anidulafungin and cilofungin.

Candida albicans accounts for more than half of the yeasts identified as the cause of infection after HCT. *Candida tropicalis* is the second most common cause of infection after HCT. Other *Candida* species that are common causes of infection after HCT are *Candida glabrata, Candida krusei, Candida lusitaniae,* and *Candida guilliermondi. Aspergillus* sp. are by far the most common cause of mold infections following HCT with *Aspergillus fumigatus* the most prevalent of the *Aspergillus* species. Other *Aspergillus* species that commonly cause infection following HCT are *Aspergillus flavus,* and *Aspergillus niger.*

Using acceptable methods for determining the in vitro activity of micafungin against clinical isolates of *Candida* sp. and *Aspergillus* sp. the following MIC values were demonstrated. As can be seen *C. albicans* and *C. glabrata* are more susceptible to micafungin than are *C. parapsilosis* and *C. tropicalis.* For the *Aspergillus* species all the isolates that were tested are inhibited by similar concentrations of micafungin.

The in vitro activity of micafungin against *Candida species* and *Aspergillus species*

Organism	Number of Isolates	MIC (µg/mL)		
		Range	MIC$_{50}$	MIC$_{90}$
C. albicans	85	0.016 - >8	0.25	0.5
C. glabrata	24	0.125 - >8	0.25	0.5
C. tropicalis	21	0.25 - >8	0.5	2
C. parapsilosis	16	0.03	>8	>8

C. krusei	8	0.06 - 2	ND	ND
A. fumigatus	40	0.0078 -0.0313	0.0156	0.0313
A. niger	11	0.0078 - 0.0625	0.0156	0.0313
A. flavus	11	0.078 - 0.0625	0.0156	0.0313
A. terreus	6	0.0039 - 0.0156	0.0078	0.0156

Information was presented by the Applicant as to the fungicidal activity of micafungin against both *Candida* species and *Aspergillus* species. Micafungin is not fungicidal against *Aspergillus* sp. and the information provided does not provide enough data to determine if micafungin is fungicidal against *C. albicans*. Micafungin is not fungicidal against *C. parapsilosis*, *C. tropicalis*, and *C. guilliermondii*.

The Applicant provided limited information on mechanisms by which fungi may become resistant to micafungin. They provided information to show there is no cross- resistance between micafungin and azoles but they did not provide cross-resistance information between micafungin and other candins.

From the pharmacokinetic information provided it appears that using the dose and the dosing schedule proposed by the Applicant that concentrations of micafungin can be achieved in the plasma that would be sufficient to inhibit the growth of yeasts and molds that had micafungin MIC_{90s} of ≤ 0.5 µg/mL.

The Applicant did not provide any animal data on the use of micafungin prophylactically to prevent *Candida albicans* or *Aspergillus fumigatus* infections. They did provide information of the micafungin treatment of immunocompromised mice and rabbits infected with *C. albicans* and *A. fumigatus*. From the data provided it appeared that micafungin was successful in reducing the number of infecting organisms and prolonging the survival of the infected animals. However, it should be noted that these animals were infected with isolates of *C. albicans* and *A. fumigatus* that were susceptible to low concentrations of micafungin. It is difficult to extrapolate the results of animal experiments to human results and when the experiments are done with a limited number of organisms that are susceptible to low concentrations of a drug it is even more difficult. The value of the experimental animal data provided by the Applicant for predicting whether

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prophylactic administration of micafungin would be successful in preventing fungal infections in humans is of limited value.

The Applicant provided information from one pivotal clinical study on the efficacy of micafungin to prevent fungal infections in HCT patients. The data from this study according to the Applicant's analysis showed that micafungin was successful in preventing fungal infections in 81% (313/386) of adult and 69% (27/39) of pediatric patients. There were 7 cases of proven/probable breakthrough infections in the micafungin arm. In the proven infection category there were six cases of breakthrough infections (1 *C. albicans*, 1 *C. lusitaniae*, 1 *C. tropicalis*, 1 *C. parapsilosis*, *1 Fusarium species*, 1 *Zygomyces* species). The breakthrough *C. lusitaniae, C. albicans, C. tropicalis,* and *C. parapsilosis* were all isolated from blood cultures. There were micafungin susceptibility test results for only two *Candida* species from the proven infection group. Both of these, as determined by in vitro susceptibility testing, had micafungin MICs that would place them in a susceptible category. The reason for the appearance of these organisms could not be determined from the information provided in the application. Two of the breakthrough organisms (*Fusarium* species, *Zygomycetes*) in the micafungin arm are organisms known not to be susceptible to micafungin.

It appears from the limited data provided by the Applicant in the pivotal study that micafungin has the potential to prevent fungal infections with *C. albicans*, certain *Candida* species and *Aspergillus fumigatus*. However, it is the feeling of this Reviewer that from the microbiology information provided in this application that a final conclusion can not be made on the efficacy of micafungin to prevent   ―   , in adult   ―   , patients undergoing hematopoietic stem cell transplantation. More clinical data is needed.

INTRODUCTION:

Due to the advancements in medical treatment (e.g. immunosuppressive regimens for the treatment of autoimmune diseases, intensive cancer chemotherapy) and diseases of the immune system (e.g. AIDS) the number of immunocompromised patients has increased in recent years. These patients because of their compromised immune status are more susceptible to infections by a variety of microorganisms. One group of microorganisms that cause infections in these patients is the fungi. The fungi that most commonly cause infections are *Candida albicans*, *Candida* species and non-*Candida* yeasts with *Aspergillus* species infections increasing in numbers over the last decade (1, 2). The immunocompromised population with profound and/or prolonged neutropenia is most susceptible to infections by fungi. In addition, non-neutropenic patients can also be at risk of *Candida* infections due to prolonged hospitalization, use of central venous catheters, and the use of multiple antibiotics, steroids, and parenteral hyperalimentation (3). Infections with yeasts, such as *C. albicans* and filamentous fungi such as *Aspergillus* species are associated with significant morbidity and mortality (1, 2, 3, 4, 5).

The current standards of care to prevent *Candida* infections in susceptible patient populations are appropriate patient care and infection control practices and prophylaxis with an antifungal agent. Fluconazole (Diflucan®) is the only prophylactic antifungal therapy currently approved for use in bone marrow transplant patients to prevent infections with yeast (6). Published studies suggest that the prophylactic use of fluconazole decreases the occurrence of proven systemic *Candida* infections, and reduces the number of deaths due to *Candida* infections in bone marrow transplant recipients, neutropenic cancer patients, and patients with acute leukemia (7, 8, 9, 10). Fluconazole is effective against many *Candida* species, however, *Candida krusei* and *Candida glabrata* are inherently resistant and a number of other species have become resistant to fluconazole (11). Fluconazole is not effective against *Aspergillus* species (6, 12).

The Applicant in this submission provides information about a new antifungal drug (micafungin) that they feel can be used

Micafungin (WF11899A) is lipopeptide antibiotic isolated from the culture broth of *Coleophoma empetri* in 1989 and chemically modified in 1994 to decrease its hemolytic activity and enhance its antifungal activity. It was at this time that its name was changed to FK463. FK463 also became known as micafungin. It is an echinocandid-type lipopeptide that is water-soluble. Micafungin acts against fungi

by inhibiting the enzyme 1,3-β-D-glucan synthase [E.C.2.4.1.34. UDP-glucose: 1,3-β-D-glucan 3-β-glucosyl transferase], an enzyme involved in the synthesis of 1,3-β-D-glucan a critical component of the cell wall of fungi. Micafungin has structural similarities with echinocandin and pneumocandin derivatives, that are also inhibitors of (1,3)-β-D-glucan synthase. 1,3-β-D-glucan while present in the cell wall of fungi is not present in mammalian tissue cells therefore micafungin should have no or extremely limited toxicity against mammalian cells.

Epidemiology of Fungal Infections in Patients Undergoing Hematopoietic Stem Cell Transplantation:

The term "Hematopoietic stem cell transplantation" (HCT) refers to bone marrow transplant. It is a more preferable term than "bone marrow transplant" because it more accurately describes the current state of transplantation, which may involve harvesting donor cells from peripheral blood, umbilical cord blood or bone marrow (13).

Candida species are normal commensal organisms that reside on mucosal membrane surfaces. Local or systemic disease occurs when the normal host-commensal relationships, particularly at the GI lining, are disrupted. The use of broad-spectrum antibiotics may result in an overgrowth of yeast, which increases the likelihood of infection and death with these yeast organisms. Mucositis due to the conditioning regimen or graft-versus-host disease disrupts the integument of the GI (or other mucous membranes such as the genital tract) leading to portals of entry for these organisms into the bloodstream. Infection with herpes simplex virus or CMV can also facilitate access of yeast organisms to otherwise sterile body sites of the body. It is not unusual to see overgrowth of yeast on the base of the viral ulcers, which enhances the chance that the yeast will cause systemic infection. Because neutrophils are required to maintain the normal integument of the GI lining and are the first line of defense against *Candida* species neutropenia is an important risk factor for the development of systemic candidiasis. The visceral organs are a common location for disseminated candidiasis, which suggests that much of the access of *Candida* species to these organs is through the portal circulation with the liver and spleen serving as a filter for the organisms. This may explain why many cases of hepatosplenic candidiasis occur in the absence of positive blood cultures. The kidney is also a common, though less frequent, site of visceral disease. Invasive candidiasis above the diaphragm is unusual. *Candida* species, however, are the second most common cause of central nervous system (CNS) infection in the HCT setting, infection in the CNS results from dissemination via the blood stream. Infection in the skin is also observed, although infrequently, in the HCT setting and is usually seen in the setting of fungemia (14).

Candida albicans accounts for more than half of all candidal species identified as the cause of infection after HCT (15). *Candida tropicalis* is the second most common cause of fungal infection in HCT patients (15, 16, 17). Infections due to *Candida glabrata, Candida krusei, Candida lusitaniae,* and *Candida gulliermondi* are seen less commonly (14). The incidence of invasive candidal infection varied from 10 to 20% before the use of fluconazole prophylaxis (18). With the introduction of fluconazole in the early 1990s the incidence of *C. albicans* and *C. tropicalis* has dropped substantially (by as much as 50% in some studies) while the incidence of other non-ablicans *Candida* species (e.g. *C. glabrata, C. parapsilosis*) is increasing (14, 16). While the frequency of occurrence of the different candidal species may have changed over the recent years it is not clear that this has been due to the use of fluconazole since this change had also been seen in centers where fluconazole had not been used (16, 19, 20). In addition, the increase of non-albicans *Candida* species was noted more than 10 years ago, before fluconazole was available (21). The incident of non-*Candida* yeasts (e.g. *Cryptococcus* spp., *Rhodotorula* spp.) as a cause of infections in HCT patients is low (14).

Aspergillus spp. are by far the most common cause of mold infections in HCT patients with *Aspergillus fumigatus* the most prevalent of the *Aspergillus* spp. Other *Aspergillus* that commonly are the cause of infections in HCT patients are *Aspergillus flavus,* and *Aspergillus niger.* The molds found less commonly as causes of infection in immunocompromised patients are the Mucorales order (e.g. *Rhizopus, Rhizomucor,* and *Absidia*) as well as a variety of less common molds such as *Fusarium, Bipolaris,* and *Pseudoallescheria.* The dimorphic fungi (e.g. *Histoplasma capsulatum, Coccidiodes immitis*) are very rare causes of infections in HCT patients' (14).

The incidence of invasive aspergillosis varies from 10 to 20% depending on the center reporting the data. Several investigators have reported a consistent increase in recent years (22, 23). In contrast to candidal infection, molds are not normal commensals in most individuals and infection with them results from colonization or inhalation of spores into the respiratory tract. Thus the pattern of distribution of mold infections is quite different from that observed for the *Candida* species. Most of the infections with *Aspergillus* species and other molds occur in the sinuses and lungs. As infection progresses, invasion of the blood vessels in the pulmonary vasculature may occur, resulting in the infection of the heart or CNS. *Aspergillus* species are the most common cause of CNS infection in the HCT setting (24). CNS infection can also develop from direct extension from the sinuses and may extend to the periorbital area as well. Only late in the course of the infection do *Aspergillus* species spread to the abdominal visceral organs (14).

IN VITRO

10

In Vitro Activity of Micafungin:

<u>Mechanism of Action</u>:

Micafungin is a water-soluble, semi-synthetic, lipopeptide of a new class of antifungal agents known as 1,3-beta-D-glucan synthase inhibitors. Other members of the class include caspofungin (Cancidas®) anidulafungin and cilofungin. These drugs act by inhibiting 1,3-beta-D-glucan synthase, an enzyme essential for the synthesis of the fungal cell walls. This class of antifungal agents has activity against *Candida* and *Aspergillus* species.

The fungal cell is considered an essential and specific target for antifugal drugs for several reasons: (i) it accounts for about 25% of the fungal cell; (ii) it is a physically rigid layer that protects the fungal cell wall from it environment; (iii) it is essential for fungal life since without a cell wall or with an altered cell wall, a fungus cannot survive; (iv) it is mainly composed of polysaccharides such as β1-3 glucans or chitin that do not exist in humans.

The Applicant has provided data (CTD Module 2.6.2, Figure 4, Company Report CRE010070, and reference 25) that indicates that micafungin inhibits the synthesis of 1,3-beta-D-glucan, an essential polymer that provides rigidity and osmotic/structural integrity to the cell wall of fungi. This mechanism of action is unique to this class of antifungals; other antifungals such as polyenes and azoles affect the synthesis of the integrity of the fungal cell membrane (26). The exact mechanism by which inhibition of the synthesis of 1,3-β-D glucan occurs is not fully understood. It is postulated that inhibitors, such as micafungin, diffuse into the membrane towards the glucan synthase or perturb the fungal membrane environment that causes inactivation of membrane bound glucan synthesis activities. It is believed that the lipid component of the lipopeptide echinocandins is critical for its activity suggesting a direct interaction with the fungal membrane. *Candida* and *Aspergillus* species exposed to micafungin demonstrate thin walls, abnormal septa formation, inhibition of germination and hyphal extension, swelling and abnormal extension of hyphal tips, and lysis (26). Mechanism based toxicity with 1,3-β-D-glucan synthase inhibitors is unlikely, according to the Applicant, since 1,3-β-D-glucan is present in fungal cell walls but not in mammalian cells (25).

The Applicant provided data (CTD Module 5.3, 5.3.5.4.2:Microbiology Report pg. 25 and Company report CRE010133) that demonstrates the activity of micafungin against *C. albicans* and *A. fumigatus*. The experiments were done using vitality- and mortality-specific fluorescent dyes. The experiments showed the morphological changes that occur to both *C. albicans* and *A. fumigatus* when they are exposed to various concentrations of micafungin. The morphological

changes that occurred suggest that the cell wall of the microorganisms were effected in some manner.

<u>In Vitro Susceptibility Test Methods:</u>

Culture conditions that may effect the results of in vitro susceptibility testing were investigated by the Applicant (CTD Module 5.3, 5.3.3.4.2 pg. 39). In evaluating the effects of culture conditions on the MIC the test method used for *C. albicans* and other yeasts was that of the NCCLS (27) and a modification of this method for testing *Aspergillus fumigatus* (28). The test broths used were as specified in the National Committee for Clinical Laboratory Standards (NCCLS) documents. The Applicant found that inoculum size had minimal effect (a two-fold decrease or increase in the MIC) on the MIC for the three species of *Candida* and the *A. fumigatus* tested. Increase in pH by one unit from the recommended pH of 7 had no effect on the MICs of the *Candida* species tested while a pH of 6 decreased the MIC by one two-fold dilution for 2 of the 3 *Candida* tested. For the *A. fumigatus* tested a 16-fold increase in the MIC at pH 8 was noted while a decrease in the pH to 6 decreased the MIC one two-fold dilution. Addition of either human serum or human serum albumin increased the MIC values in all tested species. The increase in MIC depended on the amount of serum present. The increase ranged from 16 to 64x the MIC with no serum present. The effect of serum is most likely explained by the fact that micafungin is highly protein bound (>99%).

Testing of the fungi during phases 1 and 2 (Tables 3 and 4) of micafungin development was conducted at the Medicinal Biology Research Laboratory, Fujisawa Pharmaceutical Co., Ltd., Osaka, Japan. According to the information provided by the Applicant the yeast were tested by the method recommended by the NCCLS (27). The Applicant provided the methodology used for performing the susceptibility testing in the laboratory mentioned (Company Report CRE010069). A review of the methodology used to perform the susceptibility testing of filamentous fungi by Medicinal Biology Research Laboratory revealed that the method was similar to the method now recommended by the NCCLS for testing the activity of antifungal agents against filamentous fungi such as *Aspergillus* species (28). In the opinion of this Reviewer the method is acceptable for producing reliable results based on today's knowledge of antifungal susceptibility testing.

Testing of fungi isolated from patients during the prophylaxis study (Study 98-0-050) were done under the direction of ⸺ , MD, FACP of the ' ⸺ ⸺. , , Table 21). The Applicant provided information that Dr. ⸺ used the NCCLS method for susceptibility testing of yeast (27) and a modification of this method for susceptibility testing of filamentous fungi. A description of the method Dr.

laboratory used to perform susceptibility testing of filamentous fungi showed it to be very similar to the NCCLS method (28) that was published at a later date (CTD Module 2.7.2, methodology validation, Company document 2001020113). Dr. ⸺ is an advisor to the NCCLS committee that was responsible for developing the methodology which was published in their document for the susceptibility testing of filamentous fungi (28). This Reviewer feels that Dr. ⸺ method because it is very similar to the NCCLS (28) would produce results similar to the NCCLS method (28) for susceptibility testing of filamentous fungi.

Quality Control of Susceptibility Testing:

The Applicant provided information on the quality control that was done during susceptibility testing. This information showed that the quality control procedures recommended by the NCCLS were done (27, 28) during the phase 1 and 2 studies as well as during the testing of isolates from the Phase 3 clinical prophylaxis study (CTD Module 5.3, 5.3.3.4.2 pg. 9).

CONCLUSION:

The methods used to perform antifungal in vitro susceptibility testing as described by the Applicant in this submission are currently recognized methods for doing this type of susceptibility testing. It should be recognized however, that these methods were not originally developed for determining the in vitro activity of candins, such as micafungin. Recent papers (29) have suggested that the composition of the medium can have an effect on the MIC obtained for micafungin. Also investigators who are involved with the development of the NCCLS method for in vitro susceptibility test methods for yeast (27) have questioned whether the method developed by the NCCLS for susceptibility testing of yeast is a suitable method for testing glucan synthesis inhibitors (30).

The NCCLS method for the susceptibility testing of yeasts has shown a limited ability to identify amphotericin B-resistant *Candida* and *Cryptococcus* isolates (31, 32). The ability of the NCCLS method to detect micafungin-resistant *Candida* species is undetermined at this time.

In addition, no studies to date have validated the concept of routine susceptibility testing as a means of guiding antifungal therapy. Many investigators point out that the ability to generate a MIC is of little value without the corresponding ability to interpret its clinical meaning. However, interpreting the clinical meaning of a MIC is far from straightforward because (1) MICs are not a physical measurement, (2) host factors play a critical role in determining clinical outcome, (3) susceptibility in vitro does not uniformly predict clinical success in vivo, and (4) resistance in vitro, will often, but not always, correlate with treatment failure

(30, 33). In fact some investigators feel that for critically ill patients infected with *Candida* species the net state of immunosuppression and acute physiology score of the host are more important prognostic determinants than the susceptibility of the *Candida* to an antifungal agent (31).

Micafungin Spectrum of Activity:

A literature search done by this Reviewer revealed the publication of an article on the susceptibility of *Candida* species to micafungin by an investigator not associated with studies in this NDA. In vitro susceptibility testing of the yeast isolates was performed by a broth microdilution according to the guidelines recommended by the NCCLS (27). As seen in Table 1 this study provides information on the in vitro activity of micafungin against a variety of *Candida* species (34). The investigator also determined the in vitro activity of micafungin against *Candida* species that had a decreased susceptibility to fluconazole and/or itraconazole. As can be seen in Table 2 the MIC_{90s} for *C. albicans* and *C. tropicalis* with a decreased susceptibility to fluconazole and/or itraconazole were slightly higher than for the isolates that did not have a decreased susceptibility to these drugs.

A literature search by this Reviewer could not find a paper by independent investigators on the activity of micafungin against *Aspergillus* species.

Table 1. The in vitro activity of micafungin against
Candida bloodstream isolates from cancer patients

Organism	Number of Isolates	MIC (μg/mL)		
		Range	MIC_{50}	MIC_{90}
C. albicans	85	0.016 - >8	0.25	0.5
C. glabrata	24	0.125 - >8	0.25	0.5
C. tropicalis	21	0.25 - >8	0.5	2
C. parapsilosis	16	0.03	>8	>8
C. krusei	8	0.06 - 2	ND	ND

Table 2. The in vitro activity of micafungin against
Candida species bloodstream isolates from cancer

Patients with decreased susceptibility to fluconazole
and/or itraconazole

Organism	Number of Isolates	MIC (µg/mL)		
		Range	MIC_{50}	MIC_{90}
C. albicans	15	0.125 - >8	0.25	1
C. glabrata	22	0.125 - 0.5	0.25	0.5
C. tropicalis	12	0.25 - >8	0.5	4
C. krusei	8	0.06 - 2	ND	ND

The Applicant has provided the data (CTD Module 5.3, 5.3.5.4.2:Microbiology
Report) for the antimicrobial activity of micafungin against reference strains of
fungi seen in Tables 3 and 4. Testing of the fungi noted in Tables 3 and 4 was
conducted at the Medicinal Biology Research Laboratory, Fujisawa
Pharmaceutical Co., Ltd., Osaka, Japan.

Table 3. In vitro activity of micafungin and other antifungal agents
against a variety of reference strains of fungi.

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Organism	MIC(μg/mL)			
	FK463	FLCZ	ITCZ	AMPH-B
Candida albicans ATCC90028	0.0156	0.5	0.0313	0.5
Candida albicans FP633	0.0313	0.25	0.0313	0.25
Candida tropicalis TIMM0313	0.0313	4	0.125	0.5
Candida glabrata ATCC90030	0.0156	16	1	0.5
Candida kefyr ATCC28838*	0.125	0.5	0.0625	0.5
Candida krusei ATCC6258	0.125	32	0.25	1
Candida guilliermondii 13003	8.25	2	0.25	0.5
Candida parapsilosis ATCC22019	2	2	0.25	0.5
Candida stellatoidea IFM5491	0.0313	0.125	0.0078	0.0625
Saccharomyces cerevisiae ATCC9763	0.125	2	0.25	0.5
Cryptococcus neoformans TIMM0354*	>64	0.5	0.0313	0.25
Trichosporon cutaneum D-M0340	>64	8	0.5	2
Trichosporon asahii TIMM3344	>64	2	0.25	0.25
Aspergillus fumigatus TIMM0063*	0.0078	>64	0.5	0.5
Aspergillus niger ATCC6275*	0.0078	>64	0.5	0.25
Aspergillus nidulans IFM53609*	0.0078	32	0.0625	1
Aspergillus flavus ATCC9643*	0.0156	>64	0.25	1
Aspergillus terreus IFM40852*	0.0156	>64	0.125	1
Aspergillus versicolor IFM41406*	0.0156	32	0.0625	0.5
Fusarium solani IFM41532*	>64	>64	>8	0.25
Pseudallescheria boydii IFM41585*	>64	16	0.5	1
Cladosporium trichoides IFM4821**	0.5	4	0.0078	0.25
Exophiala dermatitidis IFM4827**	2	4	0.0625	0.125
Exophiala spinifera ATCC18218**	0.25	8	0.0313	0.125
Fonsecaea pedrosoi ATCC44356**	2	16	0.125	0.5
Absidia corymbifera IFM40776	>64	>64	0.25	0.25
Cunninghamella elegans IFO4447	>64	>64	0.5	0.5
Rhizopus oryzae IFM40105	>64	>64	0.5	0.25
Rhizopus microsporus var. *rhizopodiformis* IFM46417	>64	>64	0.5	0.125

MIC values were determined by broth microdilution method according to the M27-A guideline
Medium : RPMI1640 165 mM MOPS (pH 7.0)
Inoculum : 1.0 to 2.5 × 10³ cells/ml.
Culture : 35 C (30 C) 2days (*3days, **more than 4days)
MIC : Minimum inhibitory concentration
MIC assessment :
　　Yeast : FK463, AMPH-B : Minimum drug concentration which completely inhibited visible growth
　　　　FLCZ, ITCZ : Minimum drug concentration resulting in prominent decrease in turbidity
　　　　compared with growth control
　　Aspergillus species : Minimum drug concentration resulting in prominent decrease in turbidity
　　compared
　　　　with growth control

Table 4 shows data the Applicant provided on the in vitro activity of micafungin against clinical isolates of *Candida* (CTD Module 5.3, 5.3.3.4.2:Microbiology Report).

Table 4. Activity of micafungin and other antifungal agents against clinical isolates of *Candida* species and other yeasts.

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Organism (no. of isolates)	Compound	MIC range (µg/mL)	MIC50 (µg/mL)	MIC90 (µg/mL)
C. albicans (55)	FK463	0.0078 - 0.0625	0.0156	0.0313
	FLCZ	0.0625 - 4	0.25	0.5
	ITCZ	0.0078 - 0.125	0.0313	0.0625
	AMPH-B	0.0625 - 1	0.5	0.5
C. albicans (FLCZ resistant) (4)	FK463	0.0156 - 0.0313	0.0156	0.0313
	FLCZ	16 - >64	64	>64
	ITCZ	1 - >8	>8	>8
	AMPH-B	0.25 - 0.5	0.5	0.5
C. tropicalis** (42)	FK463	0.0156 - 0.0625	0.0313	0.0625
	FLCZ	0.0625 - >64	0.25	2
	ITCZ	0.0078 - 2	0.0625	0.5
	AMPH-B	0.125 - 1	0.5	0.5
C. glabrata (36)	FK463	0.0156 - 0.0625	0.0156	0.0313
	FLCZ	1 - >64	4	32
	ITCZ	0.125 - >8	0.5	1
	AMPH-B	0.125 - 1	0.5	1
C. krusei (11)	FK463	0.125	0.125	0.125
	FLCZ	1 - 64	32	32
	ITCZ	0.125 - 1	0.5	1
	AMPH-B	1	1	1
C. parapsilosis (28)	FK463	0.5 - 4	1	4
	FLCZ	0.125 - 4	0.5	1
	ITCZ	0.0313 - 0.5	0.125	0.5
	AMPH-B	0.125 - 1	0.5	1
C. guilliermondii (29)	FK463	0.25 - 8	1	2
	FLCZ	1 - 16	4	8
	ITCZ	0.125 - 1	0.5	1
	AMPH-B	0.125 - 1	0.5	0.5
C. neoformans* (20)	FK463	>64	>64	>64
	FLCZ	0.5 - 8	4	4
	ITCZ	0.0313 - 0.5	0.25	0.5
	AMPH-B	0.25 - 0.5	0.5	0.5
C. tnianum (22)	FK463	64	64	64
	FLCZ	0.125 - 4	1	2
	ITCZ	0.125 - 0.5	0.5	0.5
	AMPH-B	0.5 - 8	2	4

MIC values were determined by broth microdilution method according to the M27-A guideline
Medium : RPMI1640-165 mM MOPS (pH 7.0)
Inoculum : 1.0 to 2.5 × 10³ cells/mL.
Culture . 35°C, 2days (*3days, **1 to 2days)
MIC : Minimum inhibitory concentration
MIC assessment :
　FK463, ABPH-B : Minimum drug concentration which completely inhibited visible growth
　FLCZ, ITCZ : Minimum drug concentration resulting in prominent decrease in turbidity compared with
　　growth control
MIC range : The range of MIC for isolates tested
MIC50 or MIC90 : The MICs at which 50 or 90 % of isolates are inhibited

Table 5 shows the summary data provided by the Applicant on the MIC$_{50s}$ and MIC$_{90s}$ obtained for micafungin against a variety Candida species. Results are presented for those organisms for which there were at least 10 isolates tested. Testing was done in the laboratory of   —
　　　　　　　　— The study was done between 12Jul95 and 28Dec99 as part of a NIAID Mycoses Study Group project (CTD Module 5.3, 5.3.5.4.2: Microbiology Report pg. 72). Testing followed the NCCLS standard M27-A microdilution method (27). Endpoint readings were done at both 24 and 48 hours and the endpoint was taken as either 50% (prominent reduction) in growth or 95% (total) reduction in growth. This was done because the M27-A protocol had been based on the reading the results of azole and flucytosine testing (48hrs/MIC50) and amphotericin B testing (48hr/MIC95) not on the testing

of candins such as micafungin. These experiments were done to determine if the time at which the test was read and the endpoint (50% or 95% inhibition of growth) that was used influenced the MIC results for micafungin. The results indicate that these factors do not influence the micafungin MIC values.

Dr. Rex concluded the following about micafungin in this report (CTD Module 5.3, 5.3.5.4.2: Microbiology Report pg. 5).

5.7.   Micafungin

The most relevant endpoint is not known for this drug. But, no matter how the MIC is measured, most isolates have an MIC of 0.03-0.06 µg/ml . The exception, as is typical for all echinocandins, is *C. parapsilosis*, which has MICs of 0.5-4 µg/ml.. *C. krusei* and *C. lusitaniae* also tend to have slightly higher MICs (0.25-1 µg/ml.) at the more restrictive endpoints. Testing with supplemental glucose was not examined, but this pattern otherwise mimics the pattern seen for anidulafungin.

Table 5. Summary of MIC$_{50}$s and MIC$_{90}$s for micafungin

Micafungin, RPMI

Hour	Endpoint	Species	N	MIC50	MIC90
24	50	Candida albicans	(731)	0 03	0.03
		Candida dubliniensis	(18)	0 03	0.03
		Candida glabrata	(458)	0 03	0.03
		Candida krusei	(49)	0 13	0 25
		Candida lusitaniae	(20)	0.03	0.13
		Candida parapsilosis	(391)	0.5	1
		Candida tropicalis	(306)	0.03	0.03
		Total	(1996)	0 03	0.5
24	95	Candida albicans	(731)	0 03	0.03
		Candida dubliniensis	(18)	0 03	0.06
		Candida glabrata	(458)	0 03	0 13
		Candida krusei	(49)	0.25	0.25
		Candida lusitaniae	(20)	0 06	0.25
		Candida parapsilosis	(391)	1	4
		Candida tropicalis	(306)	0 03	0.06
		Total	(1996)	0 03	1
48	50	Candida albicans	(731)	0 03	0 03
		Candida dubliniensis	(18)	0.03	0.03
		Candida glabrata	(458)	0 03	0.06
		Candida krusei	(50)	0 13	0.25
		Candida lusitaniae	(20)	0 06	2
		Candida parapsilosis	(391)	1	2
		Candida tropicalis	(306)	0 03	0.06
		Total	(1997)	0.03	1
48	95	Candida albicans	(731)	0 03	0 03
		Candida dubliniensis	(18)	0 03	0.06
		Candida glabrata	(458)	0 03	0.06
		Candida krusei	(50)	0 25	0 25
		Candida lusitaniae	(20)	0 13	2
		Candida parapsilosis	(391)	2	4
		Candida tropicalis	(306)	0 03	0.06
		Total	(1997)	0 03	2

Table 6 shows data the Applicant has provided on the in vitro activity of micafungin against clinical isolates of *Aspergillus* species (CTD Module 5.3, 5.3.5.4.2:Microbiology Report). The susceptibility testing of these clinical isolates was done by Medicinal Biology Research Laboratory, Fujisawa Pharmaceutical Co., Ltd., Osaka, Japan. The Applicant provided the methodology by which this testing was done (CRE 010069). The method used was a modification of the

method used for the susceptibility testing of yeast organisms. A review of the methodology used to perform the susceptibility testing of filamentous fungi by Medicinal Biology Research Laboratory revealed that the method was similar to the method now recommended by the NCCLS for testing the activity of antifungal agents against filamentous fungi such as *Aspergillus* species (28).

Table 6. Activity of micafungin and other antifungal agents against *Aspergillus* species.

Organism (no. of isolates)	Compound	MIC range (μg/mL)	MIC$_{50}$ (μg/mL)	MIC$_{90}$ (μg/mL)
A. fumigatus (40)	FK463	0.0078 - 0.0313	0.0156	0.0313
	FLCZ	8 - >64	64	>64
	ITCZ	0.0625 - 1	0.5	1
	AMPH-B	0.25 - 2	1	2
A. niger (11)	FK463	0.0078 - 0.0625	0.0156	0.0313
	FLCZ	64 - >64	>64	>64
	ITCZ	0.5 - 1	1	1
	AMPH-B	0.5 - 2	1	1
A. flavus (11)	FK463	0.0078 - 0.0625	0.0156	0.0313
	FLCZ	2 - >64	64	>64
	ITCZ	0.0625 - 0.5	0.25	0.5
	AMPH-B	0.25 - 2	2	2
A. terreus (6)	FK463	0.0039 - 0.0156	0.0078	0.0156
	FLCZ	4 - >64	16	>64
	ITCZ	0.0625 - 0.25	0.125	0.25
	AMPH-B	0.25 - 2	0.5	2

MIC values were determined by broth microdilution method according to the M27-A guideline
Medium : RPMI1640 165 mM MOPS (pH 7.0)
Inoculum : 1.0 x 10^4 cells/mL
Culture : 35°C, 3days
MIC : Minimum inhibitory concentration
MIC assessment : Minimum drug concentration resulting in prominent decrease in turbidity compared with
        growth control
MIC range : The range of MIC for isolates tested
MIC$_{50}$ or MIC$_{90}$: The MICs at which 50 or 90 % of isolates are inhibited

CONCLUSION:

The data submitted in this NDA and scientific publications support the fact that micafungin has in vitro activity against *C. albicans*, non-*C. albicans*, and *Aspergillus* species as determined by standardized in vitro susceptibility tests. This activity is at low concentrations of micafungin. There are, however, certain species of *Candida* (e.g. *C. lusitaniae, C. parapsilosis*) and certain other fungi (e.g. *Cryptococcus neoformans, Trichosporon cutaneum, Fusarium solani*) that inherently have decreased susceptibility to micafungin as shown by the higher concentrations of micafungin that are required to inhibit their growth (Tables 1, 2, 3, 4, 5, and 6). Because of the fact that certain species of *Candida* have an inherently decreased susceptibility to micafungin it would be appropriate to include this information in the label.

Spectrum of Activity of Micafungin Metabolites:

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The Applicant has indicated that at least 12 metabolites of micafungin have been identified. The Applicant, however, indicates that only two of the metabolites (M-1 and M-2) have any significant in vitro antifungal activity (CTD Module 5.3, 5.3.5.4.2: Microbiology Report pg. 13). A third metabolite named M-5 also exists. M-5 is the predominate metabolite in plasma but against *Candida* and *Aspergillus* species the Applicant states that it has $1/128^{th}$ of the activity of the parent compound. The metabolite identified as M-1 exhibited 4- to 16- fold less activity against *Candida* and *Aspergillus* species than micafungin and has moderate activity against *Cryptococcus neoformans* and *Trichosporn cutaneum*. The parent compound did not inhibit either the *C. neoformans* of *T. cutaneum*. The in vitro spectrum of activity of the second metabolite named M-2 has an in vitro spectrum and activity similar to the parent compound. In man, only trace amounts of the metabolites M-1 and M-2 were found (<1%) after a single dose. Maximum concentrations of M-1 and M-2 at steady state were not greater than 4% and 1% respectively, of the micafungin concentration after a 200-mg/day administration. Additionally, at steady state, AUC_{0-24} values for M-1 and M-2 were approximately 10% to 2% of the micafungin AUC_{0-24} values across all doses. The Applicant feels that these concentrations of M-1 and M-2 do not contribute to the therapeutic activity of the parent drug in man.

Table 7 shows the activity of the metabolites against *Candida* and *Aspergillus* species. The activity of the metabolites against the yeast and filamentous organisms was done in the same manner as the parent compound and was done at the Medicinal Biology Research Laboratory, Fujisawa Pharmaceutical Co., Ltd., Osaka, Japan (See "In Vitro Susceptibility Test Methods" above).

Table 7. Activity of the metabolites of micafungin against *Candida* and *Aspergillus* species.

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Organism		MIC (mcg/mL)			
		Micafungin	M-1	M-2	M-5
Candida albicans	ATCC90028	0.0078	0.0625	0.0078	8
Candida tropicalis	TIMM0313	0.0313	0.25	0.0313	32
Candida glabrata	ATCC90030	0.0156	0.125	0.0313	32
Candida kefyr	ATCC28838+	0.0625	1	0.125	64
Candida krusei	IFM5460	0.125	1	0.25	>64
Candida parapsilosis	IFM5774	0.5	4	1	>64
Candida guilliermondii	IFM5491	0.0156	0.0625	0.0313	16
Saccharomyces cerevisiae	ATCC9763	0.0625	0.5	0.125	>64
Cryptococcus neoformans	TIMM0354+	64	16	64	>64
Trichosporon cutaneum	IFM40140	64	16	64	64
Aspergillus fumigatus	TIMM0063+	0.0078	0.125	0.0156	1
Aspergillus niger	ATCC6275+	0.0156	0.0625	0.0078	4
Aspergillus flavus	ATCC9643+	0.0156	0.25	0.0156	16
Aspergillus terreus	IFM40852+	0.0156	0.125	0.0156	4
Aspergillus nidulans	IFM5369+	0.0156	0.125	0.0156	8
Aspergillus versicolor	IFM41406+	0.0156	0.125	0.0156	2

Study conducted at Medicinal Biology Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., Osaka, Japan.
Medium. RPMI 1640 165 mM MOPS (pH 7.0), inoculum size 1.0 - 2.5 × 10³ cells/ml, culture 35°C, 2 days (±3 days), mcg/ml, microgram per milliliter
MIC values were determined by broth microdilution according to the National Committee for Clinical Laboratory Standards M27-A guidelines [1997]
MIC assessment: yeast - minimum drug concentration which completely inhibited visible growth (I-K4o³, M-1, M-2, M-5), Aspergillus species - minimum drug concentration resulting in prominent decrease in turbidity compared with growth control
mcg, microgram, MIC, minimum inhibitory concentration
Source. CRE010075

CONCLUSION:

From the data presented in this submission the metabolites M1, M2 and M5 would not seem to play a significant part in inhibiting the growth of *C. albicans*, *Candida* species, and *Aspergillus* species in vivo.

Minimal Fungicidal Activity:

Minimum fungicidal concentrations (MFC) for micafungin were determined based on plate counts and defined as the concentration that resulted in killing of >99% of the original inoculum (CTD Module 5.3, 5.3.3.4.2). As with in vitro susceptibility testing of antifungal agents the determination of fungicidal concentrations face all of the issues of standardization that occur with determining the MIC (27, 28). The MFC_{50s} and MFC_{90s} of these clinical isolates was done by Medicinal Biology Research Laboratory, Fujisawa Pharmaceutical Co., Ltd., Osaka, Japan (CRE 100069). A review of the methodology used to determine the fungicidal concentrations of micafungin suggest that it would produce acceptable results. Table 8 shows the minimal fungicidal activity of micafungin and other antifungal agents against *Candida* species and *A. fumigatus*. As can be seen in Table 8 micafungin appears fungicidal against fluconazole-susceptible and fluconazole-resistant strains of *C. albicans* used in these experiments. It also appears fungicidal against *C. glabrata*. Micafungin was not fungicidal after 24 hours

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against *C. parapsilosis*, *C. tropicalis* and *C. guilliermondii* organisms that generally have reduced susceptibility to micafungin. From the MIC_{90} data presented in this application it would also seem reasonable that micafungin would not be fungicidal against *C. lusitaniae* because of its high MIC_{90} after 48 hours of incubation (see Table 5). Micafungin was not fungicidal against the strains of *A. fumigatus* tested.

Table 8. Minimal fungicidal activity of micafungin and other antifungal agents against *Candida* species and *Aspergillus fumigatus*.

Organism (No. of isolates)	Compound	MFC range (mcg/mL)	MFC_{50} range (mcg/mL)	MFC_{90} range (mcg/mL)
C. albicans (12)	FK463	0.0156 - 4	0.0313	0.25
	FLCZ	>64	>64	>64
	ITCZ	>8	>8	>8
	AMPH B	0.5 - 1	0.5	1
C. albicans (FLCZ resistant) (4)	FK463	0.0156 - 0.5	0.0313	0.5
	FLCZ	>64	>64	>64
	ITCZ	>8	>8	>8
	AMPH B	0.5 - 2	0.5	2
C. tropicalis (12)	FK463	0.0313 - >64	0.0625	>64
	FLCZ	0.25 - >64	>64	>64
	ITCZ	0.0625 - >8	>8	>8
	AMPH B	0.25 - 2	1	2
C. glabrata (15)	FK463	0.0156 - 0.0313	0.0156	0.0313
	FLCZ	4 - >64	>64	>64
	ITCZ	0.5 - >8	>8	>8
	AMPH B	1 - 2	1	2
C. krusei (10)	FK463	0.125 - 0.25	0.125	0.25
	FLCZ	64 - >64	>64	>64
	ITCZ	1 - 8	1	8
	AMPH B	1 - 2	1	2
C. parapsilosis (10)	FK463	2 - 16	4	8
	FLCZ	16 - >64	>64	>64
	ITCZ	0.5 - >8	8	>8
	AMPH B	1 - 4	2	2

Organism (No. of isolates)	Compound	MFC range (mcg/mL)	MFC_{50} range (mcg/mL)	MFC_{90} range (mcg/mL)
C. guilliermondii (10)	FK463	1 - >64	8	>64
	FLCZ	>64	>64	>64
	ITCZ	>8	>8	>8
	AMPH B	0.5 - 2	1	1
A. fumigatus (19)	FK463	>64	>64	>64
	FLCZ	64 - >64	>64	>64
	ITCZ	0.25 - 4	1	2
	AMPH B	1 - 4	2	4

FK463: micafungin; FLCZ: fluconazole; ITCZ: itraconazole; AMPH B: amphotericin B; mcg/ml microgram per milliliter. CFU: colony-forming unit, MFC: minimum fungicidal concentration
Medium: RPMI 1640/165 mM MOPS (pH 7.0), inoculum: 1.0 to 2.5 x 10³ cells/ml.
MFC determination: 100 mcl. of sample transferred from MIC microtiter plates to Sabouraud dextrose agar plates and incubated for ≥72 hours, MFC assessment, minimum drug concentration at which growth of less than 1 CFU was observed (more than 99% of the original inoculum was killed)
MFC range: The range of MFC for isolates tested. MFC_{50} or MFC_{90}, the MFCs at which 50% or 90% of isolates are inhibited, respectively.
Source: Company Report CRE010069

CONCLUSION:

The applicant has provided data to show that against the strains of C. albicans (fluconazole susceptible and fluconazole resistant), C. glabrata and C. krusei tested micafungin appears fungicidal. However against isolates of C. parapsilosis and C. tropicalis micafungin was not fungicidal. It is also speculated by this Reviewer that micafungin may not be fungicidal against all isolates of C. lusitaniae because of a high MIC_{90} for an isolate that was presented in this submission (Table 5).

In the opinion of this Reviewer it is unclear about the fungicidal activity of micafungin against various Candida species, including C. albicans. While the data that has been submitted indicates that certain species of Candida have inherently reduced susceptibility to micafungin resulting in micafungin not being fungicidal against these organisms it is unclear as to what percentage of C. albicans micafungin is not fungicidal against. More clinical isolates need to be tested to determine if micafungin can be considered fungicidal against C. albicans, and other species of Candida.

Mechanism(s) of Resistance:

The Applicant also provided data to show that when a strain of C. albicans (ATCC 900028) was serially transferred 15 times in the presence of subinhibitory concentrations of micafungin that the MIC was not dramatically changed. In these experiments the MIC went from 0.0156 mcg/mL to 0.0312 mcg/mL (CTD Module 5.3, 5.3.3.4.2: Microbiology report pg. 47-48). The methodology used for these experiments is provided in Company report CRE 10069. The methodology for showing whether organisms would become resistant to micafungin if passaged in the presence of subinhibitory concentrations of micafungin was similar to the methodology seen in the literature and other IND and NDA submissions. While these experiments provide in vitro information on the potential of an organism becoming resistant to micafungin whether or not an organism will become resistant in vivo can not be easily determined from such experiments.

The Applicant did not provide any information on the use of Saccharomyces cervisae and Schizosaccharomyces pombe mutants that have been used to study mechanisms of resistance to echinocandins (35, 36).

The Applicant did not provide their opinion on possible ways that fungi might become resistant to micafungin. In the opinion of this Reviewer it is possible that fungi may become resistant or develop decreased susceptibility to micafungin by a variety of methods. These methods could be a modification in the target site, increased levels of expression of the gene that controls the synthesis of the 1,3-beta-D-glucan synthase and/or overexpression of efflux genes CDR1, CDR2 and

MDR1. Such mechanisms of resistance have been described for other antifungal drugs. In the case of azole drugs, including fluconazole that targets lanosterol 14α-demethylase, the product of the ERG11 gene, antifungal drug resistance has been associated with point mutations and increased levels of expression of the ERG11 gene. Overexpression of efflux pump genes has also been shown to cause a decrease in the susceptibility of yeasts to fluconazole. Such mechanisms of resistance have been demonstrated in *C. albicans* isolated from patients being treated with fluconazole (37). In the case of *A. fumigatus* a point mutation or overexpression of the gene (FKS) that encodes the putative catalytic subunit of β-1-3 glucan synthase (38) could be the reason for this organism to develop decreased susceptibility to micafungin.

The Applicant also provided data to show that fluconazole-resistant *Candida* isolates were not cross resistant to micafungin (CTD Module 5.3, 5.3.3.4.2: Microbiology report pg. 47). Cross-resistance between fluconazole and micafungin most likely will not occur because of the different mechanisms of action of these two antifungal agents. The azoles, such as fluconazole inhibit the synthesis of the cell membrane of the fungus and micafungin inhibits the synthesis of the cell wall of fungus. The Applicant did not provide information as to whether there was cross- resistance between micafungin and other candins.

Post Antibiotic Effect (PAE):

The Applicant did not provide any information on PAE for micafungin.

Intracellular Activity of Micafungin:

The Applicant did not provide any information on the intracellular activity of micafungin.

Micafungin in Combination with other Antifungals:

The Applicant provided information from both their own experiments and the published literature about the activity of micafungin in combination with other antifungals. A summary of their in-house experiments with a combination of azoles and micafungin and amphotericin B and micafungin follows (Company report CRE010076):

In vitro interactions between FK463 and amphotericin B (AMPH-B), itraconazole (ITCZ), or fluconazole (FLCZ) were evaluated by using a checkerboard method based on the standard broth microdilution method M27-A recommended by the NCCLS. When FK463 was combined with AMPH-B, ITCZ, and FLCZ, additive interaction was observed for 41%, 85%, and 85% of *Candida albicans* isolates, respectively, and either synergistic or additive interaction was observed for 67%, 87%, and 13% of *Aspergillus fumigatus* isolates, respectively. No antagonism was observed in any combination for *C. albicans* and *A. fumigatus*. An excellent interaction was observed for *Cryptococcus neoformans* when FK463 was combined with AMPH-B, which was synergistic for 67% and additive for 33% (totality was 100%) of isolates tested. The interaction between FK463 and FLCZ was indifferent for *C. neoformans*. Antagonism was observed only in the FK463-ITCZ combination for *C. neoformans* (83%).

A literature summary provided by the Applicant of the activity of micafungin in combination with other antifungal drugs is seen in Table 9. It can be seen that according to published papers micafungin tends to have additive to synergistic activity with amphotericin B, itraconazole, fluconazole, and voriconazole both in vitro and in animal models of fungal infections.

Table 9. Literature summary provided by the Applicant of the activity of micafungin in combination with other antifungal drugs.

Reference	Organism	Assay Method	Results
Chiou et al, 2000	16 isolates of filamentous fungi, including: *A. fumigatus* *A. flavus* *A. terreus* *A. niger* *F. solani* *Rhizopus oryzae*	NCCLS broth macrodilution method/ Checkerboard inhibitory assay	The median MEC of micafungin (FK463) against the four species of *Aspergillus* was 0.25 mcg/mL (range 0.05-0.5 mcg/mL); the median MECs for *F. solani* and *R. oryzae* were >512 mcg/mL. Median MIC values of nikkomycin Z were 32 mcg/mL (*A. fumigatus*), 0.5 mcg/mL (*R. oryzae*), and >512 mcg/mL (other *Aspergillus* species and *F. solani*). Checkerboard inhibitory assay demonstrated synergy of micafungin and nikkomycin Z against *A. fumigatus* and indifference in *A. flavus, A. terreus, A. niger,* and *F. solani*. The effect in *R. oryzae* was additive to indifferent. Substantial hyphal damage was observed in *A. fumigatus*, confirming the synergism observed.
Kohno et al, 2000	20 clinical isolates of *A. fumigatus* mouse model invasive pulmonary aspergillosis	Broth microdilution method and checkerboard titration	Synergistic and additive effects for the combinations of micafungin (FK463) + amphotericin B, micafungin (FK463) + itraconazole and micafungin (FK463) + flucytosine, were observed in 65% (13/20), 45% (9/20), and 55% (11/20) of strains, respectively. These same combinations were antagonistic in 5% (1/20), 15% (3/20), and 20% (4/20) strains, respectively. Significantly higher survival rate (p<0.001) and a lower fungal burden in the lungs (p<0.001) in mice treated with micafungin (FK463) and amphotericin B compared with either agent alone
Manavathu et al, 2001	Conidial suspensions of 10 clinical isolates of *A. fumigatus*	Checkerboard; ^{14}C-amino acid incorporation	Based on growth inhibition and a calculated susceptibility index, micafungin (FK463) + amphotericin B and showed synergy while micafungin (FK463) + voriconazole showed an additive effect.

Reference	Organism	Assay Method	Results
Petraitis et al, 1999	*Aspergillus* species	Checkerboard, timed kill, and MTT assays	The combination of micafungin (FK463) (0.002-128 mcg/mL) and amphotericin B (0.015-4 mcg/ml.) was neither synergistic nor antagonistic over a range of therapeutic concentrations in vitro or in rabbits.
Stevens, 1999	10 clinical isolates of *Aspergillus*, including: *A. fumigatus*, *A. flavus*, *A. terreus*, *A. niger*	Broth macrodilution checkerboard testing	MIC, MEC, and MFC values were <16, ≤0.06, and >16 mcg/ml. respectively, for micafungin and 4->16, 2->8, and 8->16 mcg/ml. for liposomal amphotericin B (AmBisome). No antagonism was seen in any of the 10 strains. All 10 strains showed indifference, but in 7/10, there was a trend towards synergy.

MEC. minimum effective concentration, MIC: minimum inhibitory concentration, MFC: minimum fungicidal concentration; NCCLS. National Comittee for Clincial Laboratory Standards; mcg/ml.: microgram per milliliter

CONCLUSION:

From the information provided in this NDA and the scientific literature it appears that micafungin has the potential to be used in conjunction with other antifungals. The testing of combinations of antifungal drugs is not a standardized method. The same issues of standardization that occur with MIC determinations apply to the testing of combinations of antifungals. Also, the correlation of in vitro results with clinical outcome is not known.

HUMAN AND ANIMAL STUDIES

Pharmacokinetics/Pharmacodynamics:

Pharamcokinetics:

Studies to asses the protein binding of micafungin to human serum albumin (HSA) at variable concentrations of micafungin (10 -100 µg/mL) and HSA (0.5 to 4%) were done. Protein binding was determined by an ultrafiltration technique. At a HAS concentration of 4% the micafungin binding to HSA was calculated to be 99.66%, 99.68%, and 99.69% at micafungin concentrations of 10, 30 and 100 µg/mL (Module 2.7.2 Summary of Pharmacology Studies pg. 13-14).

A number of pharmacokinetic studies were done to determine the pharmacokinetic parameters of micafungin (Module 2.7.2 Summary of Pharmacology Studies pg. 33-37). The results of these studies are shown in Table 10. Study FJ-463-0001 showed a linear relationship to dose for the C_{max} and AUC over the range of 2.5 to 50 mg. Less than 1% of the administered dose was excreted in the urine. Study 97-0-400 showed that plasma micafungin concentrations declined in a biexponential manner, with a mean terminal elimination $t_{1/2}$ of 13.6 hours (with a curve estimated over 0-48 hours). Plasma

micafungin concentrations were not detectable beyond 48 hours in five of six subjects. Analysis of fecal samples pooled up through 168 hours showed that micafungin accounted for 26.8% of the total radioactivity in feces collected throughout the 168 hours. Study FJ-463-0002 that was a repeat-dose pharmacokinetic study of micafungin was conducted in Japan in 9 healthy volunteers (aged 20-29 years). Six of these subjects received 25 mg (approximately 0.405 mg/kg) of micafungin in physiological saline for 7 days. The other three subjects received physiological saline. Mean micafungin pharmacokinetic parameters are shown in Table 10. Micafungin plasma concentrations in this study are best described by a linear two-compartment model, with a steady state achieved by day 4. C_{max} values occurred at the end of the infusion and increased from day one (1.91±0.20 mcg/mL) to day 7 (2.46±0.27 mcg/mL). The elimination $t_{1/2}$ following the last dose was 14.6±1.5 hours. The day 7 AUC was 29.6±4.6 mcg•h/mL, and total clearance was 0.222±0.027 mL/min/kg. Urinary excretion of unchanged micafungin was very low. Study FJ-463-0004 was a study that compared the pharmacokinetics in 10 healthy elderly (aged 66-78 years) and 10 healthy non-elderly (aged 20-24 years) Japanese volunteers. This study concluded that there was no significant difference between elderly and non-elderly subjects for C_{max}, $t_{1/2}$, or clearance.

In conclusion these studies show:

- The maximum plasma concentrations (C_{max}) and area under the concentration-time curve (AUC) values are dose proportional in healthy volunteers following a single micafungin dose of 2.5-50 mg or 25-150 mg.
- The pharmacokinetics of micafungin were similar in healthy elderly and healthy young Japanese volunteers.

Table 10. Summary of results of pharmacokinetic studies with micafungin.

Study (No. Subjects)	Regimen	Dose (mg) [n]	C_{max} (mcg/mL)	AUC_{admin} (mcg·h/mL)	$t_{1/2}$ (h)	V_{ss} (L/kg)	Cl (mL/min/kg)
Healthy volunteers							
FJ-463-0001 (n=27)	Single 2-hour IV infusion	2.5 [3]	0.202±0.005	2.78±0.27	11.6±2.0	0.215±0.038	0.225±0.008
		5 [6]	0.397±0.045	6.45±0.70	13.7±0.7	0.224±0.024	0.201±0.024
		12.5 [6]	0.947±0.044	17.11±1.22	15.2±0.9	0.242±0.024	0.197±0.021
		25 [6]	1.865±0.310	32.63±4.18	14.8±1.2	0.239±0.023	0.201±0.025
		50 [6]	3.361±0.277	60.93±7.32	15.2±0.5	0.237±0.021	0.192±0.022
97-0-048 (n=6)	Single 1-hour infusion of ^{14}C-FK463	FK463 28.3 [6] Radioactivity‡	2.97±0.38 2.29±0.21	42.4±5.1 109.6±16.5	13.6±0.7 92.8±7.1	0.169±0.012 0.391±0.027	0.146±0.009 0.057±0.004
FJ-463-0002 (n=9 (3 received saline control))	Once daily 1-hour IV infusion for 7 consecutive days	25 [6] Day 1	1.91±0.20	26.7±5.9	---	---	---
		Day 4	2.39±0.28	---	---	---	---
		Day 7	2.46±0.27	---	14.6±1.5†	---	0.222±0.027
Table continued on next page							

Study (No. Subjects)	Regimen	Dose (mg) [n]	C_{max} (mcg/mL) [90% CI]	AUC_{admin} (mcg·h/mL) [90% CI]	$t_{1/2}$ (h)	V_{ss} (L/kg)	Cl (mL/min/kg) [90% CI]
FJ-463-0005 (n=30)	Single 0.5-hour infusion	25 [6]	2.52±0.28	14.1±5.8	14.0±1.2	0.232±0.017	0.199±0.027
		50 [6]	5.23±0.38	74.1±6.2	14.2±1.2	0.226±0.17	0.190±0.014
		75 [6]	7.90±1.35	106.5±13.4	13.3±0.7	0.225±0.020	0.203±0.015
	Single 1-hour infusion	150 [6]	14.30±1.31	216.6±23.1	14.0±0.9	0.229±0.012	0.196±0.013
	Group mean all single doses	25-150 [24]	---	·	13.9±1.0	0.228±0.016	0.197±0.018
	Once daily 1-hour infusion for 7 consecutive days	75 [6] Day 1	7.64±0.93	101.3±11.1	14.3±0.8	0.229±0.022	0.193±0.021
		Day 4	10.21±1.38	161.6±19.6	15.2±1.0	---	0.181±0.022
		Day 7	10.87±1.53	159.7±21.6	14.0±0.7	---	0.176±0.022

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Study (No. Subjects)	Regimen	Dose (mg) [n]		C_{max} (mcg/mL)	$AUC_{infinity}$ (mcg·h/mL)	$t\frac{1}{2}$ (h)	V_{ss} (L/kg)	CL (mL/min/kg)
Adult Patients								
		12.5 [8]	Day 1	0.87±0.16	12.42±2.06	11.3±2.0	0.247±0.057	0.253±0.045
		12.5 [7]	Day 7	3.85±7.33	19.35±13.04	9.9±1.8	0.222±0.101	0.264±0.113
		25 [9]	Day 1	1.86±0.87	24.04±9.16	13.2±2.2	0.239±0.045	0.213±0.045
		25 [8]	Day 7	4.81±2.72	36.38±10.57	13.8±4.0	0.238±0.075	0.199±0.033
		50 [9]	Day 1	3.66±1.26	47.12±13.77	12.7±1.8	0.243±0.059	0.222±0.047
		50 [7]	Day 7	6.42±5.70	63.81±15.77	12.5±2.6	0.215±0.067	0.200±0.052
97-8-041 (n=74 [12 received saline control])	Once daily 1-hour IV infusion for at least 7 days	75 [8]	Day 1	9.19±6.30	68.18±21.13	13.1±3.3	0.259±0.068	0.241±0.086
		75 [8]	Day 7	8.29±4.75	108.35±54.39	13.2±4.4	0.273±0.093	0.285±0.232
		100 [7]	Day 1	30.89±56.47†	157.74±148.43†	14.6±3.2	0.254±0.109†	0.206±0.097†
		100 [5-6]	*Day 1*	*6.93±1.97 [5]‡*	*102.29±24.73 [6]‡*	*---*	*0.256±0.075 [6]‡*	*0.232±0.076 [6]‡*
		100 [7]	Day 7	28.23±22.91	164.92±73.49	13.9±3.1	0.269±0.080	0.212±0.056
		150 [10]	Day 1	14.09±6.40	152.24±55.62	12.2±1.9	0.246±0.089	0.231±0.070
		150 [8]	Day 7	17.63±8.42	233.94±77.21	13.1±2.5	0.251±0.082	0.229±0.079
		200 [8]	Day 1	18.29±16.89	193.09±166.61	15.0±3.6	0.271±0.053	0.216±0.053
		200 [8]	Day 7	26.52±20.73	336.95±193.87	15.9±4.8	0.264±0.059	0.195±0.027

† The data include all patients/group. However, the extreme variability precluded rational pharmacokinetic comparisons. The extreme variance in all probability was due to sampling contamination as reflected in the Cmax, the mean values for derived parameters (AUC, V, and Cl) were also affected.
‡ Mean values for Cmax (Patients 063-502 and 063-511) as well as AUCinfinity, Vss, and Cl (Patient 063-511) were thus recalculated dropping the named patient(s) (corrected data shown below dotted line in italics)
--- Not done.

Studies done in adult subjects with severe renal dysfunction and moderate hepatic dysfunction showed there are no apparent differences in any of the mean pharmacokinetic estimates of micafungin between age-, weight, and sex-matched healthy subjects (Study 01-0-110 and Study 01-0-111, Module 2.7.2 Summary of Pharmacology Studies pg. 37-39).

Subjects with Intrinsic Factors of Interest							
FJ-463-0004 Healthy elderly (n=20)	Single 1-hour infusion	50 [10 elderly HV] 50 [10 non-elderly HV]	4.97±0.60 4.95±0.56	71.5±9.0 76.6±9.4	14.9±1.0 15.2±0.9	0.239±0.027 0.228±0.016	0.200±0.028 0.185±0.019
01-0-110 Severe Renal dysfunction (n=18)	Single 1-hour infusion	100 [9 renal dys] 100 [9 HV]	8.7±2.85 8.2±1.39 [81.9, 128.3]	118.8±33.4 123.8±17.1 [77.6, 112.3]	14.2±1.5 14.8±1.8	0.202±0.025 0.190±0.030	0.180±0.029 0.163±0.027
01-0-111 Moderate Hepatic dysfunction (n=16)	Single 1-hour infusion	100 [8 hepatic dys] 100 [8 HV]	6.9±1.86 8.8±1.80 [62.5, 97.8]	98.2±19.4 127.5±26.3 [64.7, 92.3]	14.4±0.8 15.1±2.6	0.208±0.035 0.195±0.028	0.180±0.022 0.161±0.029 [97.2, 130.1]

A pediatric study (98-0-043 Company report 2001000694- Module 2.7.2 Summary of Pharmacology Studies pg. 55-57) to determine the safety and pharmacokinetics of micafungin in febrile neutropenic pediatric patients was carried out in patients aged 2 to 17 years of age. These patients had febrile neutropenia induced by cytotoxic chemotherapy with or without bone marrow or peripheral stem cell transplantation.

A total of 78 patients received at least one dose of micafungin and 72 patients had evaluable pharmacokinetics: 0.5 mg/kg/day (n=16), 1.0 mg/kg/day (n=16), 1.5 mg/kg/day (n=12), 2.0 mg/kg/day (n=12), 3.0 mg/kg/day (n=9), and 4.0 mg/kg/day (n=7). Intravenous micafungin was administered daily as a one-hour infusion beginning within 24 hours of the initiation of antibacterial therapy for

febrile neutropenia for up to 4 weeks duration. Patients had serial blood samples drawn for pharmacokinetic assessment on days 1 and 4.

The results of this study can be seen in Table 11. Mean plasma micafungin concentration vs. time profiles declined in a biexponential manner and were not appreciably different on days 1 and 4 in patients aged 2-17 years old. The mean terminal elimination $t_{1/2}$ was approximately 11.9-15.2 hours over the study and did not vary over time. Mean AUC_{0-24} values were relatively dose proportional on days 1 and 4; the mean accumulation was 1.4. Mean Cl and V_{ss} values were essentially constant with dose and time, ranging from 0.240-0.333mL/min/kg and 0.225-0.344 L/kg, respectively. The pharmacokinetic profiles obtained on days 1 and 4 for the two age cohorts, 2-12 and 13-17 years, were relatively consistent with mean data derived from the entire population. However, individual CL values were evaluated as a function of age and revealed that pediatric patients 2-8 years had micafungin Cl values 1.5-2-fold greater than the rates in patients greater than 8 years of age. Mean Cl values from the older pediatric cohort were consistent with values previously obtained from adult patients.

Table 11. Summary of pediatric pharmacokinetic study

Pharmacodynamics:

The pharmacodynamics of antifungal agents is not as well understood as the pharmacodynamics of antibacterial agents. However, there has been in recent years increasing literature on the pharmacodynamics of antifungal agents' (30). The Applicant did not provide any detailed information on the pharmacodynamics of micafungin.

In this application it is stated that micafungin inhibits 1,3-β-D-glucan synthase derived from C. albicans ATCC 90028 and A. fumigatus TIMM0063 in a concentration dependent manner (CRE010070). The inhibition kinetics between substrate and inhibitor are no-competitive (CRE010070).

Published data based on in vitro time-kill studies and animal experiments support the concept that the activity of micafungin is concentration dependent (39).

CONCLUSION:

At the Applicant's proposed dose for adults of 50 mg once daily the C_{max} at day one is approximately 3.6 µg/mL and approximately 6.4 µg/mL after 7 days. For the Applicant's proposed dose o   —   .   .   ..
approximately 11.2 µg/mL after day one and approximately 16.7 µg/mL after 4 days. With the pharmacodynamics of this drug believed to be concentration dependent these C_{max} concentrations exceed the MICs for a variety of *C. albicans*, non-*Candida albicans* and *Aspergillus fumigatus* isolates (see Tables 1, 2, 3, 4, 5, and 6). In addition the pharmacokinetics of the micafungin as presented by the Applicant suggest that it is similar in the young and elderly, febrile neutropenic patients, people with renal insufficiency, and those with moderate hepatic dysfunction. In pediatric patients the pharmacokinetic profiles obtained on days 1 and 4 for the two age cohorts, 1-12 and 13-17 years old were relatively consistent with mean data derived from the entire population. However, individual CI values elevated as a function of age revealed that patients 2-8 years old had micafungin CI values 1.5 to 2 fold greater than rates than 8 years of age. Mean CI values from the older pediatric cohort were consistent with adult values.

From the pharmacokinetic and MIC_{90} information presented in this NDA it appears that by using the adult   —   dosing schedule proposed by the Applicant concentrations of micafungin sufficient to inhibit the growth of *C. albicans*, non-*C. albicans*, *A. fumigatus* and *Aspergillus* species can be achieved in the plasma.

Animal Data:

The Applicant has submitted data about micafungin activity in chemically immunocompromised mouse and rabbit models of disseminated fungal infections (Company reports CRE 010071; CRE 010072; CRE 010073; References 40, 41, 42). The animal data pertains to animals infected with *Candida* or *Aspergillus* species and then treated with micafungin. There was no animal data presented by the Applicant were the animal had been given micafungin before being infected with either *Candida* species or *A. fumigatus*. The Applicant states the "the minimum effective plasma concentration of micafungin that significantly reduced the fungal burden in kidneys and lungs in mouse models was estimated to be 0.16 to 0.26 µg/mL for disseminated candidiasis and 0.55 to 0.80 µg/mL for pulmonary aspergillosis" (Company report CRE010073).

Table 12 shows a summary of data from experiments with immunosuppressed male Slc-ICR strain mice models of disseminated fungal infections. Micafungin

as well as the fluconazole and amphotericin B were administered intravenously for 4 days while the itraconazole was administered for four days orally. The data show that the micafungin was not as active against *C. krusei* and *C. parapsilosis* as it was against the other *Candida* species used in the experiments. The activity of micafungin against the two strains of *A. fumigatus* used in the experiments was similar to its activity against the strains of *Candida* species other than *C. krusei* and *C. parapsilosis* (Company Report CRE010071).

The data in Table 12 shows that the strain of *C. krusei* (15001) used in these experiments was more refractive to micafungin than the other strains of *Candida* other than *C. parapsilosis* that is known to have decreased susceptibility to micafungin.

Table 12. In vivo activity of micafungin and other antifungals in immunocompromised mice infected with *Candida* and *Aspergillus*.

Organism	Inoculum (CFU)	ED$_{50}$ mg/kg (95% confidence intervals)			
		FK463	FLCZ	ITCZ	AMPH B
C. albicans FP633	2.1 x 10⁴	0.18 (0.13 - 0.24)	1.54 (1.08 - 2.12)	24.0 (17.2 - 33.4)	0.07 (0.04 - 0.10)
C. albicans 16001	3.0 x 10³	0.14 (0.10 - 0.19)	2.00 (0.93 - 4.30)	23.5 (11.9 - 39.4)	0.09 (0.06 - 0.12)
C. albicans 16007	1.0 x 10³	0.18 (NC)	2.06 (1.14 - 3.49)	N.D	0.06 (0.03 - 0.09)
C. albicans FP1840	8.4 x 10³	0.38 (0.27 - 0.54)	17.2 (12.2 - 40.2)	37.2 (25.9 - 55.7)	0.16 (0.12 - 0.23)
C. glabrata 16011	4.0 x 10⁵	0.18 (0.12 - 0.26)	4.89 (3.37 - 6.97)	16.9 (10.2 - 24.0)	0.10 (0.07 - 0.13)
C. tropicalis 16004	3.6 x 10⁴	0.35 (0.26 - 0.48)	7.2 (NC)	62.0 (44.2 - 98.0)	0.21 (0.15 - 0.29)
C. krusei 15001	7.2 x 10⁵	1.61 (1.11 - 3.98)	>20.0	>80	0.71 (0.46 - 2.04)
C. parapsilosis 16005	1.4 x 10⁵	3.21 (2.22 - 7.90)	4.57 (2.85 - 6.56)	18.3 (11.4 - 26.3)	0.08 (0.06 - 0.11)
C. guilliermondii 13003	1.2 x10⁴	0.77 (0.55 - 1.08)	6.27 (4.08 - 10.1)	44.2 (31.9 - 63.6)	0.32 (0.24 - 0.45)

Table 12 (cont).

| Organism	Inoculum (CFU)	ED$_{50}$ mg/kg (95% confidence intervals)			
		FK463	FLCZ	ITCZ	AMPH B
A. fumigatus IBMM0063	1.8 X 10⁵	0.36 (0.24-0.56)	-20.0	-80.0	0.28 (0.20-0.40)
A. fumigatus IFM40835	4.0 X 10⁴	0.23 (0.15-0.35)	-20.0	-80.0	0.25 (0.18-0.36)

FK463: micafungin, FLCZ: fluconazole, ITCZ: itraconazole, AMPH B: amphotericin B, mg/kg: milligram per kilogram, N.D.: not done, NC: not calculated

Mice: 4-week old male, ICR strain, 8 mice per group, cyclophosphamide intraperitoneally administered at 200 mg/kg 4 days before and 1 day after infection

Infection: each strain of fungi suspended in saline and injected intravenously

Treatment: once daily for 4 days starting 1 hour after infection by intravenous administration (ITCZ was orally administered using the same regimen)

ED$_{50}$ calculated based on survival rate 15 days after infection by probit analysis or normal probability plot

Source: Company Report CRE010071

     In-vivo Activity against *Candida albicans*:

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The Applicant submitted data (Figure 1) that shows that the survival of ICR mice with disseminated *C. albicans* infection was prolonged with a dose of micafungin at ≥ 0.125 mg/kg (starting 1 hour after intravenous infection and administered once daily for 4 days). The higher the dose of micafungin the longer the survival time was for the infected mice. All untreated control mice died by day 11 of disseminated candidiasis (Company report CRE010071).

Figure 1. Survival of imunocompromised mice infected with *Candida albicans* after treatment with micafungin.
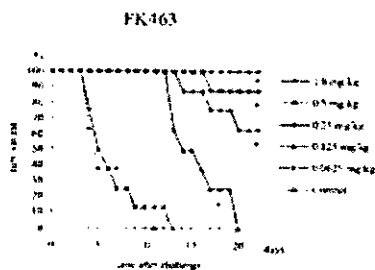
FK463. micafungin. AMPH B. amphotericin B. FLCZ. fluconazole. ITCZ: itraconazole: mg kg milligram per kilogram
Mice: male. 4-week-old ICR strain, 8 mice per group: cyclophosphamide intraperitoneally administered at 200 mg/kg 4 days before and 1 day after infection
Infection. *C. albicans* 16001 suspended in saline and injected intravenously (3.0 x 10⁴ colony forming unit)
Treatment. once daily for 4 days starting 1 hour after infection by intravenous administration (ITCZ was orally administered using the same regimen; saline was injected intravenously).
Survival rate was plotted by Kaplan-Meier plot and statistical analysis performed by Wilcoxon rank sum test against control group [significantly different from control FK463, AMPH B and FLCZ (p <0.01), ITCZ (p<0.0125). by Bonferroni correction]
Source Company Report; CRE010071

Data from the studies described in Table 13 and Figure 1 show that a single 0.5 or 1.0 mg/kg intravenous dose of micafungin administered immediately after infection significantly reduced (p<0.01) the number of viable yeast recovered from the kidney compared to the control (Company report CRE010071). In addition the Applicant has provided data (Company Report 010071) that suggests that there is no difference in the outcome in the mouse model used between starting the micafungin 1 hour or 1 day after initiation of the *C. albicans* infection.

In another series of experiments the Applicant looked at the efficacy of micafungin to treat *C. albicans* infection of the tongue and esophagus (Company Report CRE 010074). The data presented by the Applicant shows that micafungin at 2 mg/kg or higher (i.e., 5 and 10 mg/kg) significantly (p<0.05) decreased viable colony counts as compared to control.

The Applicant also presented data from a study in persistently neutropenic rabbits in which a statistically significant (p<0.05) clearance of *C. albicans* from

the liver, spleen, kidney, brain, lung and vena cava was observed compared to an untreated control (41).

In Vivo Activity against *Aspergillus*:

In experiments (Fig. 2) done with immunocompromised mice infected with pulmonary *A. fumigatus* micafungin ($\geq$0.5 mg/kg) administered daily for 4 days significantly increased (p <0.0125) 15-day survival compared to the control group (Company Report CRE010072). From these same experiments (Table 13) the ED_{50} (mg/kg) for the three strains of *A. fumigatus* used ranged from a mean of 0.26 to 0.45 mg/Kg.

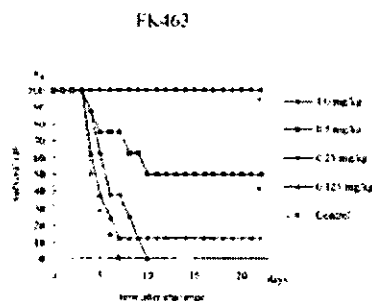Figure 2. Survival after treatment with micafungin in an immunocompromised mouse model of pulmonary aspergillosis.

Table 13. Efficacy of micafungin and other antifungals in an immunosuppressed mouse model of pulmonary aspergillosis.

Organism	Inoculum (CFU)	ED_{50} mg/kg (95% confidence interval)			
		FK463	FLCZ	ITCZ	AMPH B
A. fumigatus TIMM0063	8.0×10^3	0.33 (0.23 - 0.45)	>20	28.3 (20.5 - 38.6)	0.25 (0.16 - 0.36)
A. fumigatus IFM40835	8.3×10^3	0.26 (0.18 - 0.36)	>20	34 (41)	0.25 (0.16 - 0.36)
A. fumigatus IFM40836	7.0×10^3	0.45 (0.32 - 0.64)	>20	40.3 (28.0 - 62.4)	0.46 (0.32 - 0.76)

FK463: micafungin, FLCZ: fluconazole, ITCZ: itraconazole, AMPH B: amphotericin B, mg/kg: milligram per kilogram
Mice: male 4-weeks-old ICR strain, 8 mice per group, cyclophosphamide intraperitoneally administered at 200 mg/kg 4-days before and 1 day after infection
Infection: *A. fumigatus* suspended in physiological saline and intranasally inoculated
Treatment: once daily for 4-days starting 1.5 hours after infection by intravenous administration (ITCZ was orally administered using the same regimen)
ED_{50}: calculated based on survival rate 15 days after infection by probit analysis or normal probability plot
† Not calculated
Source: Company Report CRE010072

In addition to the data from the experiments described in Figure 2 and Table 13 the Applicant also provided information from a mouse study (40). The study showed a statistically significant prolongation of survival (p=0.01) and reduction

in *A. fumigatus* colony forming units in the brain (p=0.03) and kidney (p=0.01) of immunocompromised mice. The Applicant also provided data from a published study that showed improved survival for persistently neutropenic rabbits infected with *A. fumigatus* treated with micafungin (42). Also another study provided by the Applicant showed improved survival for profoundly neutropenic CD1 mice infected with itraconazole-resistant *A. fumigatus* or amphotericin B-resistant *Aspergillus terreus* (41).

CONCLUSION:

The results of animal models to study the efficacy of micafungin to treat *C. albicans* and *A. fumigatus* infections in immunocompromised mice and rabbits suggests that micafungin has the ability to act in vivo against these organisms. In the data presented by the Applicant the doses of micafungin that were administered to the animals were doses that correlated with what would be used as a prophylactic dose in humans. However, it should be noted that these animals were infected with isolates of *C. albicans* and *A. fumigatus* that were susceptible to low concentrations of micafungin. It is difficult to extrapolate the results of animal experiments to human results and when the experiments are done with a limited number of organisms that are susceptible to low concentrations of a drug it is even more difficult. Thus the value of the animal experiments for predicting whether prophylactic administration of micafungin would be successful in preventing fungal infections in humans is difficult to determine from the limited data provided by the Applicant.

The Applicant in this submission did not provide any animal data on the prophylactic use of micafungin to prevent fungal infections.

Human Studies

The Applicant has provided data from four studies to support their opinion that micafungin is efficacious as prophylaxis agains' ——— patients undergoing hematopoietic stem cell transplantation. Study 98-0-050 (889 patients), was a Phase 3, randomized, double-blinded study (Study 98-0-050) and three Phase 1 or 2 studies (Studies 97-0-041, 98-0-043) and FG463-21-03). Table 14 gives an overall summary of the various studies. The data that follows is the Applicant's data. It does not represent data that the Agency has evaluated. For the purposes of this review the data is being used as an overview of the efficacy of micafungin during prophylaxis studies. The reader is referred to the complete FDA review for a statistical analysis of these studies.

Table 14. Summary of clinical studies

Study No. Centers Location	Start/ Status	Design	Regimen	Objective	No. by Arm E/C	Duration	M/F Age Range Race †
98-0-050 72 locations in the United States and Canada	Nov 23 1999 C	DB R AC (stratified by center, age, type of transplant, risk for transplant-related mortality) Phase 3	1-hour infusion once daily FK463 50 mg/day (1 mg/kg/day < 50 kg weight) Fluconazole 400 mg/day (8 mg/kg/day < 50 kg weight)	E, S FK463 vs fluconazole	FK463 426/402 [397] [425] Fluconazole 463/428 [433] [457]	Infused at the time the transplant-conditioning regimen was initiated or within 48 hours post-initiation; treated until neutrophil recovery + 0 to 5 days (ANC ≥ 500 cells/mm³) or prophylactic therapy. Maximum duration of 42 days posttransplant (4-week follow-up)	FK463 M 253 (59.5%) F 172 (40.5%) Age range: 0.6-73.0 years W 387 (91.1%)/B 30 (7.1%)/O 8 (1.9%) Fluconazole M 274 (60.0%) F 183 (40.0%) Age range: 0.6-71.0 years W 411 (89.9%)/B 37 (8.1%)/O 9 (2.0%)
97-0-041 5 locations in the United States	June 10 1999 C	DB R SDE AC Phase 1 and 2	FK463/saline: 1-hour infusion once daily; fluconazole PO once daily (1-hour infusion if PO not possible) FK463 + fluconazole FK463 12.5, 25, 50, 75, 100, 150, or 200 mg/day; fluconazole 400 mg/day Fluconazole + saline 400 mg/day fluconazole, 100 mL normal saline infusion	S, PK MTD of FK463 in combination with fluconazole	FK463 + fluconazole 65/44 [57] [62] Fluconazole + saline 14/7 [11] [12]	FK463 initiated between 48 hrs prior to transplant to 24 hrs posttransplant; treated until neutrophil recovery (ANC ≥ 500 cells/mm³) or up to 5 days post recovery (up to a maximum of 4 weeks (4-week follow-up)	FK463 + fluconazole M 39 (32.3%) Age range: 19-65 years W 50 (80.6%) B 12 (19.4%) Fluconazole + saline M 5 (41.7%) F 7 (58.3%) Age range: 20-56 years W 100%

Study	Diagnosis Key Inclusion Criteria	Key Assessments/ Evaluations	Primary Endpoints	Secondary Endpoints
98-0-050	Age 26 months, scheduled to undergo autologous or syngeneic (for hematologic malignancies) or allogeneic hematopoietic stem cell transplant	Chest x-ray or CT scan, vital signs, lab profile, assessment of fungal infection, fungal surveillance cultures, fungal isolates from positive fungal cultures. Adverse events (during the study to 72 hours posttreatment)	Treatment success, defined as the absence of a proven, probable, or suspected systemic fungal infection through the end of therapy AND the absence of a proven or probable systemic fungal infection through the end of the 4-week posttreatment period	Proven or probable systemic fungal infections during the study: proven, probable, or suspected systemic fungal infection through the end of therapy; proven or probable fungal infection during the posttreatment period for patients who did not have systemic fungal infection during treatment; proven or probable fungal infection by organism; use of systemic antifungal agents posttreatment; time to treatment failure during study; time to suspected fungal infection, superficial fungal infections through the end of therapy; fungal colonization at the end of therapy.
97-0-041	Adults, undergoing autologous or allogeneic bone marrow or peripheral stem cell transplant.	Chest x-ray, vital signs, lab profile, assessment of fungal infection, cultures or biopsy. Adverse events (during the study to 72 hours posttreatment)	MTD, defined as highest dose of FK463 administered without development of same grade 3 toxicity‡ at least possibly related to study drug in 3 separate patients	Ascertainment of toxicities associated with FK463 at doses of 12.5 mg/day and greater Efficacy assessment based on incidence of systemic fungal infections through 4-week posttreatment, incidence of mortality during treatment and posttreatment, and use of additional antifungal therapy Pharmacokinetics

Study	Diagnosis Key Inclusion Criteria	Key Assessments/ Evaluations	Primary Endpoints	Secondary Endpoints
FG463-21-03	Adults scheduled to undergo bone marrow or peripheral stem cell transplantation	Vital signs, lab profile, incidence of fungal infection and adverse events (monitored continuously during treatment)	MTD, defined as the highest dose of FK463 administered without development of grade 3 or 4 toxicity‡ at least possibly related to study drug, in 23 different patients and safety profile	Efficacy as measured by the incidence of fungal infection, and pharmacokinetics.
98-0-043	Ages 2-17 years, fever, neutropenia (ANC <500 cells/mm³) AND one of the following: leukemia, lymphoma (except patients on maintenance therapy); bone marrow or peripheral stem cell transplant, chemotherapy inducing >10 days of neutropenia; aplastic anemia; or myelodysplastic syndrome.	Vital signs, chest x-ray, lab profile, assessment of fungal infection and adverse events (during the study to 72 hours posttreatment)	MTD, defined as highest dose of FK463 administered without development of ≥grade 3 toxicity‡ at least probably related to study drug in ≥2 different patients at same dose level, and safety assessments.	Efficacy was assessed based on the incidence of systemic fungal infections during treatment; during posttreatment, and a requirement for empirical therapy

Study	Diagnosis Key Inclusion Criteria	Key Assessments/ Evaluations	Primary Endpoints	Secondary Endpoints
FG463-21-03	Adults scheduled to undergo bone marrow or peripheral stem cell transplantation	Vital signs, lab profile, incidence of fungal infection and adverse events (monitored continuously during treatment)	MTD, defined as the highest dose of FK463 administered without development of grade 3 or 4 toxicity‡ at least possibly related to study drug, in ≥3 different patients and safety profile	Efficacy as measured by the incidence of fungal infection, and pharmacokinetics
98-0-043	Ages 2-17 years; fever, neutropenia (ANC <500 cells/mm³) AND one of the following leukemia; lymphoma (except patients on maintenance therapy), bone marrow or peripheral stem cell transplant; chemotherapy inducing >10 days of neutropenia, aplastic anemia; or myelodysplastic syndrome	Vital signs, chest x-ray, lab profile, assessment of fungal infection and adverse events (during the study to 72 hours posttreatment)	MTD, defined as highest dose of FK463 administered without development of ≥grade 3 toxicity‡ at least probably related to study drug in ≥2 different patients at same dose level, and safety assessments	Efficacy was assessed based on the incidence of systemic fungal infections during treatment; during posttreatment, and a requirement for empirical therapy.

Study 98-0-050 (NIAID MSG 46):

This study was a pivotal study. This study was a randomized (1:1), double-blind, phase 3 study comparing the safety and efficacy of micafungin with fluconazole for the prophylaxis of fungal infections in adult and pediatric patients (≥6 months old) scheduled to undergo an autologous or syngeneic (for hematologic malignancies) or allogeneic hematopoietic stem cell transplant. Fluconazole was chosen as the comparator therapy since it is the only antifungal therapy currently approved by the FDA for prophylactic use in bone marrow transplant patients. In this study, fluconazole was administered at the recommended approved dose for adults and a comparable, commonly used dose for children. It was administered intravenously to simplify the blinding.

The criteria for initiating empirical antifungal therapy were based on NIAID Mycoses Study Group Criteria (43). Patients had a suspected fungal infection if they were neutropenic (ANC, 500 cell/mm³), had a fever and received broad spectrum antibiotics for at least 96 hours, and required initiation of empirical systemic antifungal therapy. The definition of a proven fungal infection included patients with a biopsy from a sterile site showing invasive fungal elements (with or without culture) or a positive culture from a normally sterile site. The definition for a probable infection was a patient with a characteristic clinical and radiological picture of disseminated candidiasis or pulmonary aspergillosis; pulmonary aspergillosis also required a bronchoalveolar lavage (BAL) specimen positive histologically or by culture. These criteria are consistent with previously conducted randomized trials with fluconazole (8, 10) and were based on the recommendations established by the NIAID Mycoses Study Group (43).

The study involved 889 randomized patients of whom 882 received at least one dose of study drug. Approximately 60% of the patients in either the micafungin or fluconazole arms were male. Mean ± standard deviation for age was 43.2 ± 17.12 years in the micafungin group and 41.9 ± 17.11 years in the fluconazole group. The population of pediatric patients ($\leq$16 years of age) in the study was 84 (84/882 = 9.5%) and 6.3% (56/882) were elderly ($\geq$65 years of age). Over one-half of the patients underwent an allogeneic transplant (micafungin 220/425, 51.8%; fluconazole 256/457. 56.0%) and nearly one-third of the transplant patients were at high risk (uncontrolled malignancy [not in remission] at the time of transplantation) of transplant related mortality (micafungin 127/423. 29.9%; fluconazole 152/457, 33.3%).

In adult patients, the mean duration of antifungal prophylaxis therapy was similar between the two treatment arms; both had a median duration of approximately 18 days. The mean ± standard deviation average daily dose in mg per day was 47.5±7.83 mg/day in the micafungin arm and 374.1±68.20 mg/day in the fluconazole arm, closely approximating the targeted dose. The median duration of therapy in pediatric patients was 22 days for the micafungin arm and 21 days for the fluconazole arm. The mean ± standard deviation average daily dose in pediatric patients was 0.9 ± 0.11 mg/kg in the micafungin arm and 7.7 ± 0.66 mg/kg in the fluconazole arm, closely approximating the target dose.

The primary efficacy endpoint was treatment success, defined as the absence of a proven, probable, or suspected systemic infection through the end of therapy and the absence of a proven or probable systemic fungal infection through the end of the 4-week post-treatment period. Both criteria had to be met in order for the patient to be considered a treatment success. Suspected fungal infection was defined as a requirement for empirical systemic antifungal therapy for fever and neutropenia despite broad-spectrum antibacterial therapy.

As seen in Table 15 micafungin was at least 80% successful in achieving the primary endpoint of preventing a suspected, proven, or probable fungal infection.

Table 15. Overall Treatment Success at End of Study 98-0-05

	FK463	Fluconazole	Treatment Difference+	95% CI‡	p-value++
Full Analysis Set	340/425 (80.0%)	336/457 (73.5%)	~6.5%	(0.9%, 12.0%)	0.026
Per Protocol Set	322/397 (81.1%)	321/433 (74.1%)	·7.0%	(1.3%, 12.6%)	0.015

Full analysis set: all randomized patients who received at least 1 dose of study drug, primary analysis set
Per protocol set: all randomized patients who were deemed evaluable using strict patient classification
which included a requirement to become neutropenic, which was defined as ANC <200 cells mm³
Treatment success: absence of proven, probable, or suspected systemic fungal infection through the end of
therapy and absence of proven or probable systemic fungal infection through the end of study
+ FK463 rate fluconazole rate
‡ 95% confidence interval for the difference in overall success rate is based on the large sample normal
approximation
++ From the Cochran-Mantel-Haenszel test controlling for center
Source: Study 98-0-050 Company Report Tables 12 and 13 4.4.2

Table 16 gives the treatment success at the end of the study by age. As can be seen the success rate for pediatric patients was lower than for adults in the micafungin arm. The Applicant has speculated on the difference between the success rates for the adult and pediatric populations. They state that "Since the number of pediatric patients is small, it may be difficult to draw a definitive conclusion. However, a lower success rate in pediatric patients compared with adult patients was observed in both treatment arms in Study 90-0-050. It is likely that the lower success rate in the pediatric population compared with the adult population in Study 98-0-050 was due to the type of transplant (allogeneic versus autologous) rather than a drug associated effect" (NDA 21-506 response to FDA request for information dated August 21, 2002).

Table 16. Treatment success by study age

Age Group	FK463 (n=425)	Fluconazole (n=457)	Treatment Difference+
<16 Years	27/39 (69.2%)	24/45 (53.3%)	·15.9%
≥16 Years	313/386 (81.1%)	312/412 (75.7%)	·5.4%
≥65 Years of Age	32/33 (97.0%)	16/23 (69.6%)	·27.4%
<65 Years	308/392 (78.6%)	320/434 (73.7%)	·4.9%

Patient base: all randomized patients who received at least 1 dose of study drug (full analysis set)
Treatment success: absence of proven, probable, or suspected systemic fungal infection through the end
of therapy and absence of proven or probable systemic fungal infection through the end of study
+ FK463 rate fluconazole rate
Source: Study 98-0-050 Company Report Table 14

For those patients that did fail, the median time to failure was 17 days in both the micafungin and fluconazole treatment arms. Breakthrough systemic fungal infections in this study are summarized in tables 17 and 18. All 18 patients (7 in the micafungin arm and 11 in the fluconazole arm) who developed a confirmed proven or probable systemic fungal infection during the study had received an allogeneic transplant. Table 18 shows the organisms involved in the proven or probable fungal infections during the study. The overall incidence of breakthrough invasive fungal infections was 1.6% (7/425) for the micafungin patients and 2.4% (11/457) for the fluconazole patients. These findings are

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similar to the 2.8% incidence reported by Goodman (10) for a comparable patient population in a study with fluconazole.

Table 17. Breakthrough systemic fungal infections

Presence of Systemic Fungal Infection	FK463 (n=425)	Fluconazole (n=457)
During Entire Study (Treatment and Posttreatment)		
Overall	7 (1.6%)	11 (2.4%)
Proven	6 (1.4%)	8 (1.8%)
Probable	1 (0.2%)	3 (0.7%)
During Prophylactic Treatment		
Proven	4 (0.9%)	5 (1.1%)
Probable	1 (0.2%)	3 (0.7%)
During 4-Week Posttreatment		
Proven	2 (0.5%)	3 (0.7%)
Probable	0	0

Patient base all randomized patients who received at least 1 dose of study drug (full analysis set)
Proven: includes patients with a biopsy from a sterile site showing invasive fungal elements (with or without culture) or a positive culture from a normally sterile site.
Probable: includes patients with the characteristic clinical or radiological picture of disseminated candidiasis or pulmonary aspergillosis. pulmonary aspergillosis also required a BAL specimen positive histologically or by culture.
The case report forms for all patients with an investigator-reported proven or probable breakthrough invasive fungal infection were reviewed in a blinded manner against the protocol-specified diagnostic criteria. Source: Study 98-0-050 Company Report Table 17

Table 18. Organisms involved in proven or probable fungal infections

Organism	FK463 (n=425)	Fluconazole (n=457)
Proven	6 (1.4%)	8 (1.8%)
Aspergillus species	0	4 (0.9%)
Candida species	4 (0.9%)	2 (0.4%)
Fusarium species	1 (0.2%)	2 (0.4%)
Zygomyces species	1 (0.2%)	0
Probable	1 (0.2%)	3 (0.7%)
Aspergillus species	1 (0.2%)	3 (0.7%)

Patient base: all randomized patients who received at least 1 dose of study drug (full analysis set)
Proven: includes patients with a biopsy from a sterile site showing invasive fungal elements (with or without culture) or a positive culture from a normally sterile site
Probable: includes patients with the characteristic clinical or radiological picture of disseminated candidiasis or pulmonary aspergillosis. pulmonary aspergillosis also required a BAL specimen positive histologically or by culture.
The case report forms for all patients with an investigator-reported proven or probable breakthrough invasive fungal infection were reviewed in a blinded manner against the protocol-specified diagnostic criteria. Source: Study 98-0-050 Company Report Table 18

A total of 44 patients died during the study, 18 (4.2%) in the micafungin treatment arm and 26 (5.7%) in the fluconazole treatment arm. Three patients died of causes related to fungal infection; 2 patients in the fluconazole arm died of

pulmonary aspergillosis and 1 patient in the micafungin arm died due to infection with a *Zygomycetes*.

Study 97-0-041

This was a randomized (4:1), double-blinded, sequential group dose escalation maximum tolerated (MTD), safety and pharmacokinetic study evaluating micafungin in combination with fluconazole for prophylaxis (versus fluconazole and saline) of fungal infections in adult patients undergoing a bone marrow or peripheral stem cell transplant. Micafungin was given in combination with fluconazole because, at the time this study was initiated, there was limited prior experience with micafungin in patients. Because micafungin was administered in combination with fluconazole this study will not be discussed further in this review.

Study FG463-21-03

This study was an open-label, sequential group dose escalation; maximum tolerated dose (MTD), safety and pharmacokinetic study evaluating micafungin for prophylaxis of fungal infections in adult patients undergoing a bone marrow or peripheral stem cell transplant. Micafungin was not administered in combination with fluconazole in this study.

A total of 36 patients were enrolled in this study, all patients completed at least 8 days of therapy. The age range of patients was 19 to 65 years. Efficacy was assessed based on the incidence of fungal infections. A total of 6 of 36 patients (16.7%) developed a suspected fungal infection during treatment. Five of these infections were of the mouth and skin. There were no confirmed breakthrough invasive/systemic fungal infections during the study.

Study 98-0-043

This study was an open-labeled, sequential group, dose escalation; maximum tolerated dose (MTD), safety and pharmacokinetic study evaluating micafungin in febrile neutropenic pediatric patients (2 to 17 years of age). Two age cohorts were evaluated, 2 to 12 years of age and 13 to 17 years of age.

A total of 78 patients were enrolled in this study. Seventy-seven of the patients were evaluable. Of the 77 patients 69 were considered pediatric patients ($\leq$16 years of age). The mean duration of study drug exposure in the age group 2 to 12 was 6.6 ± 4.61 days and in the 13 to 17 years group 6.9 ± 5.47 days. The most common underlying disease was acute lymphocytic leukemia with other underlying diseases being solid tumor, acute myelogenous leukemia, and non-Hodgkin's lymphoma. Of the 35% (27/77) patients that underwent a transplant,

70% (19/27) had an allogeneic transplant and 59% (16/27) received peripheral stem cells.

A total of 27% (21/77) patients had a suspected systemic fungal infection by the end of therapy, which was defined as a patient who met their institutional criteria for initiating empirical therapy with amphotericin B. No patients had proven or probable breakthrough systemic fungal infection during therapy. During the posttreatment period the majority of patients (61%, 47/77) received no additional systemic antifungal therapy while 13% (10/77) of patients received prophylactic antifungal therapy and 27% (21/77) of patients received empirical antifungal therapy. One patient (15 year old, in the 0.5 mg/kg day micafungin treatment group) was diagnosed with a probable fungal pneumonia during the posttreatment period. Another patient (15 year old in the 0.5 mg/kg micafungin treatment group) who completed the study with no evidence of fungal infection died 19 days after completing therapy (day 33). At autopsy, a focus of aspergillosis was found in the right upper lung.

Overall Success Rates of Clinical Studies:

Table 19 gives the overall prophylaxis success for the pivotal study (98-0-050) and the other supporting studies. As can be noted the overall success rate for the pivotal study was lower for the pediatric group (69% versus 81%) of patients than for the adolescent and adult populations (>17 years of age).

Table 20 shows the breakthrough organisms for the all of the studies. Of the proven/probable fungal infections among the 600 patients receiving micafungin in these trials, there were 4 cases of candidiasis, 3 of aspergillosis, 2 of zygomycosis and 1 of fusariosis.

Table 19. Overall success in prophylaxis studies

Study	Overall	Adults	Pediatric Patients+
98-0-050 (FK463)	n = 425 340 (80.0%)	n 386 313 (81.1%)	n = 39 27 (69.2%)
98-0-050 (Fluconazole)	n = 457 336 (73.5%)	n = 412 312 (75.7%)	n = 45 24 (53.3%)
97-0-041‡† (FK463)	n = 62 47 (75.8%)	n = 62 47 (75.8%)	—
97-0-041‡ (Fluconazole)	n = 12 7 (58.3%)	n = 12 7 (58.3%)	
FG463-21-03¶	n = 36 30 (83.3%)	n = 36 30 (83.3%)	-
98-0-043	n 77 53 (68.8%)	n 8 7 (87.5%)	n = 69 46 (66.7%)

Patient base: all randomized enrolled patients who received at least 1 dose of study drug (full analysis set)
Treatment success: absence of proven, probable, or suspected systemic fungal infection through the end of therapy and absence of proven or probable systemic fungal infection through the end of study
+ Adults were defined in Study 98-0-050 as those ≥ 16 years of age. Studies 97-0-041 and FG463-21-03 were protocol-defined adult studies. Study 98-0-043 was protocol-defined as a pediatric study although patients 17 years of age were included; only patients <16 years of age are included as pediatric patients in this table
‡ Treatment was a combination of FK463 and fluconazole
¶ The design of Study FG463-21-03 did not allow for a posttreatment period
Source: Appendix Table 2.7 3.3, Efficacy Appendix Tables 1.1, 2.1, 3.1

Table 20. Proven and probable fungal infections by organism in the micafungin arm

	98-0-050 (n=425)	97-0-041+ (n=62)	FG463-21-03 (n=36)	98-0-043 (n=77)
Proven	6 (1.4%)	1 (1.6%)	0	1 (1.3%)
Aspergillus species	0			1 (1.3%)
Candida species	4 (0.9%)			
Fusarium species	1 (0.2%)			
Zygomyces species	1 (0.2%)	1 (1.6%)		
Probable	1 (0.2%)	0	0	1 (1.3%)
Aspergillus species	1 (0.2%)			1 (1.3%)

Patient base: all randomized patients who received at least 1 dose of study drug (full analysis set)
+ Treatment was a combination of FK463 and fluconazole
Source: Study 98-0-050 Company Report Section 8.2.2, Table 18. Study 97-0-041 Company Report Section 8.1, Study FG463-21-03 Section 8.1 Table 8, Study 98-0-043 Company Report Section 8.1.

Table 21 gives the species of the breakthrough organisms isolated from patients in Study 98-0-050 and their micafungin and fluconazole MICs that were provided by the Applicant. The Applicant defined the minimum fungicidal concentration (MFC) as ≥96% killing of inoculum and the minimum effective concentration (MEC) was defined as ≤2+ growth in the test well when compared to the growth control given a 4+. There were 7 incidents of breakthrough infection (6 proven and 1 probable) in the micafungin arm of the study but due to protocol deviations only four isolates were obtained for susceptibility testing. For the micafungin arm susceptibility test results are only available for 3 from the proven infection category. In the micafungin arm one of the breakthrough infections (*Zygomyeces*) occurred in the only pediatric patient (7 years of age). The age range of patients in which breakthrough infections occurred in the micafungin arm was 33 to 53 years of age.

There were 11 incidents of breakthrough infection in the fluconazole arm (8 proven and 3 probable). Due to protocol deviations only four isolates from the proven category were obtained for susceptibility testing. In the fluconazole arm there were three breakthrough infections (1 *C. parapsilosis*, 2 *Aspergillus*) in pediatric patients. The age range of patients in the fluconazole arm who experiences breakthrough infections was 9 to 67 years of age.

The reason for some of the breakthrough infections is not clear since some of the organisms that were isolated and considered breakthrough organisms are susceptible to the drug that the patient was receiving. The possibility exists that the organism that was isolated was not the actual cause of the infection. The *Fusarium* infections probably do represent true breakthrough infections since neither micafungin nor fluconazole have activity against *Fusarium*. The fact that the *A. fumigatus* isolated from the patient receiving fluconazole is resistant to both fluconazole and micafungin shows that not all strains of *A. fumigatus* may be susceptible to micafungin. Patients receiving micafungin should be carefully monitored for infections due to this organisms as well as those yeasts (e.g. *C. parapsilosis, C. guilliermondii*) against which micafungin has decreased activity.

Table 21. Study 98-0-050. Fungal organisms isolated from breakthrough infections of patients receiving micafungin or fluconazole prophylactically and their micafungin and fluconazole MICs, Minimum Effective Concentration (MEC), and Minimum Fungicidal Concentration (MFC)

Organism	Micafungin (µg/mL)			Fluconazole (µg/mL)		
	MIC	MEC*	MFC	MIC	MEC	MFC
Study 98-0-050						
Micafungin Arm						
*Candida lusitaniae***	0.125	0.125	0.5	≤0.5	≤0.5	>64
*C. albicans***	≤0.063	≤0.063	0.25	≤0.5	≤0.5	>64
*Fusarium***	>16	1	>16	>100	>100	>100
Fluconazole Arm						
*Candida krusei***	0.5	0.5	0.5	32	32	>64
Fusarium x 2***	>16	>16	>16	>100	>100	>100

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*Aspergillus fumigatus**						
	>16	$\leq$0.063	>16	>100	>100	>100

MEC = Minimum effective concentration, MFC = Minimum fungicidal concentration
*MEC $\leq$2+ growth control (control 4+)
**Proven infection
*** Two separate occurrences, organisms had same susceptibility profile. Both proven infections.

Table 22 gives susceptibility information on isolates from patients in the 98-0-050 study that could not be classified as either proven or probable infections. The *C. albicans* and the *C. glabrata* were isolated from bronchoalveolar lavage specimens. Both patients went on to clear there infections. The Applicant defined the minimum fungicidal concentration (MFC) as $\geq$96% killing of inoculum and the minimum effective concentration (MEC) was defined as $\leq$2+ growth in the test well when compared to the growth control given a 4+.

Table 22 Study 98-0-050. Micafungin and fluconazole susceptibility test results for isolates from patients that could not be categorized as proven or probable infections

Organism	Micafungin (μg/mL)			Fluconazole (μg/mL)		
	MIC	MEC	MFC	MIC	MEC	MFC
Study 98-0-050						
Micafungin Arm						
Candida albicans	0.25	0.25	0.25	>64	>64	>64
Fluconazole Arm						
Candida glabrata	$\leq$0.063	$\leq$0.063	0.5	64	64	64

MEC = Minimum effective concentration, MFC = Minimum fungicidal concentration

CONCLUSION:

The only clinical study that gives a glimpse at the potential efficacy of micafungin to prevent infections with *C. albicans*, *non-C. albicans* and *Aspergillus* species is 98-0-050. The other studies that the Applicant states in the NDA provide evidence of the efficacy of micafungin to   ―   , are insufficient from which to draw any conclusions. The studies were primarily pharmacokinetic studies.

The microbiology portion of Study 98-0-050 where cases of breakthrough fungal infections (28 incidents total) were being studied (micafungin and fluconazole arms combined) contained six 6 (6/28 = 21%) incidents of protocol deviations and 13 (13/28 = 46%) incidents were no culture was obtained. In the cases were the patients could be classified as proven or probable infections there were two cases of protocol deviation in the micafungin arm and two cases of protocol deviations in the fluconazole arm which resulted in there being no susceptibility test results for fungal isolates.

The data from study 98-0-050 according to the Applicant showed that micafungin was successful in preventing fungal infections in 81% (313/386) of adult and 69% (27/39) of pediatric patients. The Applicant has speculated on the difference between the success rates for the adult and pediatric populations. They state that "Since the number of pediatric patients is small, it may be difficult to draw a definitive conclusion. However, a lower success rate in pediatric patients compared with adult patients was observed in both treatment arms in Study 90-0-050. It is likely that the lower success rate in the pediatric population compared with the adult population in Study 98-0-050 was due to the type of transplant (allogeneic versus autologous) rather than a drug associated effect" (NDA 21-506 response to FDA request for information dated August 21, 2002).

There were 7 cases of proven/probable breakthrough infections in the micafungin arm. In the proven infection category there were six cases of breakthrough infections (1 *C. albicans*, 1 *C. lusitaniae*, 1 *C. tropicalis*, 1 *C. parapsilosis*, 1 *Fusarium species*, 1 *Zygomyces* species). The breakthrough *C. lusitaniae*, *C. albicans*, *C. tropicalis*, and *C. parapsilosis* were all isolated from blood cultures. There were micafungin susceptibility test results for only two *Candida* species from the proven infection group. Both of these by in vitro susceptibility testing had micafungin MICs that would place them in a susceptible category to micafungin. The reason for the appearance of these organisms is not known. Two of the breakthrough organisms (*Fusarium* species, *Zygomycetes*) in the micafungin arm are organisms known not to be susceptible to micafungin. The MFC values given in Table 21 and 22 relate to the amount of micafungin or fluconazole that killed $\geq$96% of the inoculum. The term MEC refers to a visual assessment of growth in a test well that shows less turbidity than the growth control well. The MEC has a rather indirect relationship to clinical outcome. How it relates to the in vivo effectiveness of an antifungal is not known. The MFC is a

term commonly used and relates to an actual plate count of organisms remaining in an antifungal concentration test well. The MFC value suggests a concentration when achieved that can cause death of the fungi. It has a more direct relationship to in vivo outcome than does MEC. However, the relation of MFC to clinical outcome is not known.

It appears from the limited data provided by the Applicant in pivotal study 98-0-050 that micafungin has the potential to prevent fungal infections with *C. albicans*, certain non-*C. albicans* and *Aspergillus fumigatus*. However, it is the feeling of this Reviewer that a final conclusion can not be made on the efficacy of micafungin to ⋅ _____ in adult and pediatric patients undergoing hematopoietic stem cell transplantation. More clinical data is needed.

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_____ Date:_____
Frederic J. Marsik, Ph.D.

CONCURRENCE ONLY:

___Albert T. Sheldon Jr. Ph.D. _____ Date:_____10/15/02_Final____
HFD-520/TLMicro/AT Sheldon, Jr.

_____ Date:_____
HFD-520/DepDir/L Gavrilovich

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_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Product Quality Microbiology Review
Review for HFD-590

23 JANUARY 2002

NDA: 21-506

Drug Product Name
    Proprietary: —
    Non-proprietary: micafungin sodium
    Drug Product Classification: Anti-Fungal Agent, systemic

Review Number: 1

Subject of this Review
    Submission Date: 29 April 2002
    Receipt Date: 29 April 2002
    Consult Date: 4 June 2002
    Date Assigned for Review: 6 January 2003

Submission History (for amendments only)
    Date(s) of Previous Submission(s): N/A
    Date(s) of Previous Micro Review(s): N/A

Applicant/Sponsor
    Name: Fujisawa Healthcare, Inc.
    Address: Three Parkway North; Deerfield, IL 60015-2548
    Representative: Robert M. Reed, Assoc. Director, Reg. Affairs
    Telephone: 847-317-8985

Name of Reviewer: Bryan S. Riley, Ph.D.

Conclusion: Approvable pending resolution of product quality
        microbiology deficiencies.

Product Quality Microbiology Data Sheet

A. **1.** **TYPE OF SUPPLEMENT:** N/A

  2. **SUPPLEMENT PROVIDES FOR:** N/A

  3. **MANUFACTURING SITE:**   Takaoka Plant
                                        Fujisawa Pharmaceutical Co., Ltd.
                                        30, Toide Sakae-machi
                                        Takaoka, Toyama 939-1118
                                        Japan

  4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND
      STRENGTH/POTENCY:** Sterile Lyophilized powder for IV infusion.
          50 mg

  5. **METHOD(S) OF STERILIZATION:**

  6. **PHARMACOLOGICAL CATEGORY:** Anti-Fungal

B. **SUPPORTING/RELATED DOCUMENTS:** N/A

C. **REMARKS:** This application was submitted electronically in the format of the
    CTD-Q.

filename: 21506.doc

Executive Summary

I.   **Recommendations**

   A.   **Recommendation on Approvability** – This submission is approvable pending resolution of product quality microbiology deficiencies.

   B.   **Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – N/A

II. **Summary of Microbiology Assessments**

   A.   **Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – The bulk drug product is

   B.   **Brief Description of Microbiology Deficiencies** – Validation of the sterilization processes was not adequately described, the holding period for the reconstituted drug product was not validated and the stability program is inadequate. See section 3 "List of Microbiology Deficiencies and Comments".

   C.   **Assessment of Risk Due to Microbiology Deficiencies** – Since the information provided in the application was deficient, a scientific evaluation of the drug product manufacturing process cannot be performed and the level of sterility assurance cannot be determined. Additionally, the in-use period for the reconstituted drug product   at room temperature) could allow microorganisms, introduced during reconstitution, to proliferate in the drug product prior to infusion. The inability of the agency to adequately evaluate the sterility assurance of this parenteral product presents at least a moderate risk to the public health from the standpoint of product quality microbiology.

III. **Administrative**

   A.   **Reviewer's Signature** _____

   B.   **Endorsement Block**
        Bryan S. Riley, Ph.D. (Microbiology Reviewer)
        Peter H. Cooney, Ph.D. (Microbiology Supervisor)

   C.   **CC Block**
        N/A

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_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

/s/
- -
Bryan Riley
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